PEM CARS

PEDIATRIC EMERGENCY MEDICINE

CRITICAL ARTICLE REVIEWS

VERSION 3.0 (2019)

NYU Langone Health

INTRODUCTION

WELCOME TO PEMCARS: 2019

The PEMCAR or Pediatric Emergency Medicine Critical Article Review originated in 2004 from my desire as a fellowship director to add a structured format to our division's journal club sessions and to provide our fellows with the opportunity to write comprehensive critical article reviews. The structure comes from completing a critical review form from the User's Guide to the Medical Literature (Amazon Link) and adding a concise article summary or "Clinical Bottom Line". The PEMCARS are distributed monthly to the faculty, fellows and residents of the departments of Pediatrics and Emergency Medicine.

This PEMCAR ebook is not intended to be a "BEST OF" or a compilation of the "PRACTICE CHANGING" articles. We recognize that our definition of these may not be the same as yours. This ebook is simply a compilation of the articles that we have reviewed. Having said that, we have tried to include many of the articles that come up frequently in clinical practice.

We have included articles from the "adult" emergency medicine literature on topics like renal stones and pulmonary embolism where there is a dearth of pediatric evidence. We have also included some studies of less than stellar methodologies. Including only the well-designed studies does not help us to identify the less than great ones.

Finally, we acknowledge that there is a lot of room to interpret some of the questions in the review forms and the clinical bottom lines that we have written. If your opinion differs from ours or if you feel we have made in error in some way, then we would be happy to hear from you.

This 2019 version includes 25 new PEMCARS bringing the total to 200. We anticipate updating this ebook on an annual basis with the articles that we have reviewed in the previous year. Feedback is always welcome.

Many thanks to the fellows of the NYU School of Medicine Pediatric Emergency Medicine Fellowship Program who have written the PEMCARs and to the faculty who have mentored them over the years

Michael

Michael Mojica, M.D.
Associate Professor of Emergency Medicine and Pediatrics
Director of Education: Division of Pediatric Emergency Medicine
New York University School of Medicine/Bellevue Hospital Center
michael.mojica@nyumc.org

PEMCAR Logo designed by Douglas Lockyer www.douglockyer.com
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5. TIPS: Tips for teaching the module
6. BLANK REVIEW FORM: A blank review form for the article type reviewed
7. COMPLETE REVIEW FORM: For the article reviewed in the module.

REVIEW FORMS

The review forms used are those from the 3rd edition of the Users' Guide to the Medical Literature. When a review form did not exist we created our own. These include the review forms for the derivation, validation and impact analysis of a clinical decision rule and the review forms for a meta-analysis of diagnostic test studies, observational studies and clinical decision rules.

Our review forms can be found at the following Dropbox Link: REVIEW FORMS

NEW PEMCARS: V3.0 (2019)

CHAPTER REORGANIZATION

The addition of over 50 new PEMCARS since the first version has resulted in a few sections with a large numbers of topics. The sections have been reorganized to improve navigability .

Orthopedic PEMCARS have been removed from the Trauma section into a separate Orthopedics section. Infection PEMCARS have been moved to their respective sections. For example, the Pneumonia PEMCARS have been moved to the Respiratory section and the Meningitis PEMCARS has been moved to the Neurology section. A new Head and Neck Infections section has been added. The procedure PEMCARS have been moved to their respective sections. For example, Laceration Repair PEMCARS has been moved to the Trauma section. Three new Procedure Sections have been added: Airway Procedures, Painful Procedures and Vascular Access

Airway Procedures: Endotracheal Intubation: Apneic Oxygenation
Apneic Oxygenation Reduces Hypoxemia During Endotracheal Intubation In The Pediatric Emergency Department
Am J Emerg Med. 2019 Jan;37(1):27-32., PubMed ID: 29699900

Airway Procedures: Rapid Sequence Intubation: BVM Ventilation
Bag-Mask Ventilation During Tracheal Intubation Of Critically Ill Adults.
N Engl J Med. 2019 Feb;380(9):811-21., PubMed ID: 30779528

Dermatology: Abscess Incision And Drainage: Antibiotics: Meta-Analysis
Systemic Antibiotics For The Treatment Of Skin And Soft Tissue Abscesses: A Systematic Review And Meta-Analysis
Gottlieb M, DeMott JM, Hallock M, Peksa GD., PubMed ID: 29530658

Emergency Medical Services: Advanced Airway Management
Effect Of A Strategy Of A Supraglottic Airway Device Vs Tracheal Intubation During Out-of-Hospital Cardiac Arrest On Functional Outcome: The AIRWAYS-2 Randomized Clinical Trial
JAMA. 2018 Aug 28;320(8):779-791., PubMed ID: 30167701

Endocrine-Metabolic: Fluid And Electrolyte Replacement
Balanced Crystalloids Versus Saline In Noncritically Ill Adults
N Engl J Med. 2018 Mar 1;378(9):819-828., PubMed ID: 29485926

Environmental Injuries: Esophageal Impaction: Glucagon Meta-analysis
Glucagon For Relief Of Acute Esophageal Foreign Bodies And Food Impactions: A Systematic Review And Meta-Analysis
Pharmacotherapy. 2019 Apr;39(4):463-472., PubMed ID: 30779190

Gastroenterology: Gastroenteritis: Probiotics
Lactobacillus Rhamnosus GG Versus Placebo For Acute Gastroenteritis In Children.
N Engl J Med. 2018 Nov 22;379(21):2002-2014., PubMed ID: 30462938

Genitourinary-Renal: Acute Kidney Injury: Contrast Nephropathy
Acute Kidney Injury After Computed Tomography: A Meta-analysis.
Ann Emerg Med. 2018 Jan;71(1):44-53.e4., PubMed ID: 28811122

Genitourinary-Renal: Urinary Tract Infection: Disposition
Management Of Urinary Tract Infections In Young Children: Balancing Admission With The Risk Of Emergency Department Revisits.
Academic Pediatrics. 2019 Mar;19(2):203-208. PubMed ID: 29864523

Infections: Febrile Neonate: PECARN Decision Rule Derivation
A Clinical Prediction Rule To Identify Febrile Infants 60 Days And Younger At Low Risk For Serious Bacterial Infections
JAMA Pediatr. 2019 Feb 18, PubMed ID: 30776077

Neurology: Febrile Seizure: Acetaminophen For Recurrence
Acetaminophen and Febrile Seizure Recurrences During The Same Fever Episode.
Pediatrics. 2018 Nov;142(5). Pii: E20181009., PubMed ID: 30297499

Neurology: Status Epilepticus: Keppra Vs Phenytoin (PREDICT)
Levetiracetam Versus Phenytoin For Second-Line Treatment Of Convulsive Status Epilepticus In Children (ConSEPT): An Open-Label, Multicentre, Randomised Trial.
Lancet. 2019 Apr 17. Pii: S0140-6736(19)30722-6., PubMed ID: 31005386

Neurology: Status Epilepticus: Keppra Vs Phenytoin (PERUKI)
Levetiracetam Versus Phenytoin For Second-Line Treatment Of Paediatric Convulsive Status Epilepticus (EcLiPSE): A Multicentre Open-Label Randomised Trial.
Lancet. 2019 Apr 17. Pii: S0140-6736(19)30724-X., PubMed ID: 31005385

Orthopedics; Forearm Fractures: Amsterdam Wrist Rule Impact
Implementation of The Amsterdam Pediatric Wrist Rules.
Pediatr Radiol. 2018 Oct;48(11):1612-1620., PubMed ID: 29992444

Procedures: Analgesia: Intranasal Fentanyl Vs Ketamine
Effect of Intranasal Ketamine Vs Fentanyl on Pain Reduction for Extremity Injuries In Children: The Prime Randomized Clinical Trial.
JAMA Pediatr. 2019 Feb 1;173(2):140-146., PubMed ID: 30592476

Respiratory: Bronchiolitis: Predictors Of Care Escalation
Predicting Escalated Care in Infants with Bronchiolitis
Pediatrics. 2018 Sep;142(3). Pii: E20174253. PubMed ID: 30126934

Resuscitation: Septic Shock: QSOFA Score Accuracy
Translating Sepsis-3 Criteria in Children: Prognostic Accuracy Of Age-Adjusted Quick SOFA Score In Children Visiting The Emergency Department With Suspected Bacterial Infection.
Front Pediatr. 2018 Oct 1;6:266., PubMed ID: 30327759

Surgery: Intussusception: Point Of Care Ultrasound Meta-Analysis
Accuracy Of Point-Of-Care Ultrasound And Radiology-Performed Ultrasound For Intussusception: A Systematic Review And Meta-Analysis
Am J Emerg Med. 2019 Jun 4., PubMed ID: 31182360

Trauma: Cervical Spine Injury: Decision Rule Re-Derivation (PECARN)
Cervical Spine Injury Risk Factors in Children with Blunt Trauma.
Pediatrics. 2019 Jul;144(1)., PubMed ID: 31221898

Trauma: Head Trauma: Hyperosmolar Therapy
Hyperosmolar Therapy in Pediatric Severe Traumatic Brain Injury: A Systematic Review.
Crit Care Med. 2019 Sep 25, PubMed ID: 31567404

Trauma: Head Trauma: Machine Learning vs PECARN Head Trauma Rules
Comparison Of Machine Learning Optimal Classification Trees With The Pediatric Emergency Care Applied Research Network Head Trauma Decision Rules.
JAMA Pediatr. 2019 Jul 1;173(7):648-656., PubMed ID: 31081856

Trauma: Hemorrhagic Shock: Pediatric Tranexamic Acid Safety
Safety Of Tranexamic Acid During Pediatric Trauma: A Nationwide Database Study.
Pediatr Crit Care Med. 2018 Dec19(12):e637-e642, PubMed ID: 30199511

Trauma: Head Trauma: Predictors Of Late Presenting TBI (PREDICT)
Delayed Presentations to Emergency Departments of Children with Head Injury: A PREDICT Study.
Ann Emerg Med. 2019 Jul;74(1):1-10., PubMed ID: 30655017

Trauma: Primary Survey: Whole Body vs Selective CT
Association Of Whole-Body Computed Tomography With Mortality Risk In Children With Blunt Trauma
JAMA Pediatr. 2018 Jun 1;172(6):542-549., PubMed ID: 29630685

Vascular Access: Peripheral Intravenous: Ultrasound Guided
Ultrasonographic Guidance To Improve First-Attempt Success In Children With Predicted Difficult Intravenous Access In The Emergency Department: A Randomized Controlled Trial.
Ann Emerg Med. 2019 Jul;74(1):19-27., PubMed ID: 31126618

NEW PEMCARS: V2.0 (2018)

Endocrine-Metabolic: Diabetic Ketoacidosis: Fluid Rate And Tonicity
Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis.
N Engl J Med. 2018 Jun 14;378(24):2275-2287. PubMed ID: 29897851

Dermatology: Abscess Incision and Drainage: Loop Drainage Technique: Meta-analysis
Comparison of The Loop Technique with Incision and Drainage for Soft Tissue Abscesses: A Systematic Review and Meta-Analysis.
Am J Emerg Med. 2018 Jan;36(1):128-133. PubMed ID: 28917436

GU-Renal: Urinary Tract Infection: UTI Risk Calculator Derivation
Shaikh N, Hoberman A, Hum SW, Alberty A, Muniz G, Kurs-Lasky M, Landsittel D, Shope T. Development And Validation Of A Calculator For Estimating The Probability Of Urinary Tract Infection In Young Febrile Children.
JAMA Pediatr. 2018 Jun 1;172(6):550-556., PubMed ID: 29710324

Infections: Febrile Neonate: Biomarker Utility
Accuracy of Complete Blood Cell Counts to Identify Febrile Infants 60 Days or Younger with Invasive Bacterial Infections.
JAMA Pediatr. 2017 Sep 11: E172927. PubMed ID: 28892537

Infections: Febrile Neonate: Urinalysis Accuracy
Accuracy Of The Urinalysis For Urinary Tract Infections In Febrile Infants 60 Days And Younger
Pediatrics. 2018 Jan 16. pii: e20173068. PubMed ID: 29339564

Neurology: Migraine Headache: Low Dose Propofol
Low-Dose Propofol for Pediatric Migraine: A Prospective, Randomized Controlled Trial
J Emerg Med. 2018 Feb 15, (18) 30015-5.PubMed ID: 29456086

OB-GYN: Ovarian Torsion: Decision Rule Derivation
Does She Have Adnexal Torsion? Prediction of Adnexal Torsion in Reproductive Age Women
Arch Gynecol Obstet. 2018 Mar; 297(3):685-690.PubMed ID: 29270727

Procedures: Endotracheal Intubation: Bougie vs ET Tube and Stylet
Effect of Use of a Bougie vs Endotracheal Tube and Stylet on First-Attempt Intubation Success Among Patients with Difficult Airways Undergoing Emergency Intubation: A Randomized Clinical Trial (Beam Trial: Bougie Use In Emergency Airway Management)
JAMA. 2018 Jun 5;319(21):2179-2189.PubMed ID: 29800096

Procedures: Endotracheal Intubation: Cricoid Pressure
Cricoid Pressure During Induction for Endotracheal Intubation in Critically Ill Children: A Report from National Emergency Airway Registry for Children.
Pediatric Critical Care Medicine. 2018 June. 19(6):528–537. PubMed ID: 29863636

Procedures: Procedural Sedation: Adverse Event Risk Factors
Risk Factors For Adverse Events In Emergency Department Procedural Sedation For Children
JAMA Pediatr. 2017;171(10):957–964.PubMed ID: 28828486
Respiratory: Bronchiolitis: Decompensation Risk Factors
Risk Factors for Respiratory Decompensation Among Healthy Infants with Bronchiolitis
Hosp Pediatr 2017 Sep;7(9):530-535.,PubMed ID: 28830913

Respiratory: Bronchiolitis: High Flow Oxygen via Nasal Cannula
A Randomized Trial Of High-Flow Oxygen Therapy In Infants With Bronchiolitis
N Engl J Med. 2018 Mar 22;378(12):1121-1131., PubMed ID: 29562151

Respiratory: Pneumonia: Point of Care Lung Ultrasound Meta-Analysis
Lung Ultrasound Compared to Chest X-Ray for Diagnosis of Pediatric Pneumonia: A Meta-Analysis.
Pediatric Pulmonology, 2018 Apr 26.,PubMed ID: 29696826

Resuscitation: Advanced Life Support: Endotracheal Intubation During Cardiac Arrest
Association Between Tracheal Intubation During Pediatric In-Hospital Cardiac Arrest and Survival
JAMA. 2016;316 (17):1786–1797.PubMed ID: 27701623

Resuscitation: Advanced Life Support: Epinephrine For Out-of-hospital Cardiac Arrest
Measuring The Effectiveness Of Drug Administration In Cardiac Arrest: A Randomized Trial Of Epinephrine In Out-of-Hospital Cardiac Arrest
N Engl J Med. 2018 Jul 18., PubMed ID: 30021076

Resuscitation: Basic Life Support: Bystander CPR In Pediatric Out Of Hospital Arrest
Association Of Bystander Cardiopulmonary Resuscitation With Overall And Neurologically Favorable Survival After Pediatric Out-of-Hospital Cardiac Arrest In The United States: A Report From The Cardiac Arrest Registry To Enhance Survival Surveillance Registry.
JAMA Pediatr. 2017 Feb 1;171(2):133-141., PubMed ID: 27837587

Resuscitation: Septic Shock: Antibiotic Timing
Delayed Antimicrobial Therapy Increases Mortality and Organ Dysfunction Duration in Pediatric Sepsis
Crit Care Med. 2014 Nov;42(11):2409-17, PubMed ID: 25148597

Resuscitation: Septic Shock: Identification Process
Improving Recognition of Pediatric Severe Sepsis in the Emergency Department: Contributions of a Vital Sign–Based Electronic Alert and Bedside Clinician Identification
Ann Emerg Med. 2017 Dec;70(6):759-768.e2., PubMed ID: 28583403

Resuscitation: Septic Shock: Lactate As A Predictor Of Mortality
Association Between Early Lactate Levels And 30-Day Mortality In Clinical Suspected Sepsis In Children
JAMA Pediatr. 2017 Mar 1;171(3):249-255., PubMed ID: 28068437

Resuscitation: Septic Shock: NY State Resuscitation Bundle Completion
Association Between the New York Sepsis Care Mandate and In-Hospital Mortality for Pediatric Sepsis
JAMA. 2018 Jul 24;320(4):358-367., PubMed ID: 30043064

Surgery: Appendicitis: Pediatric Appendicitis Risk Calculator Derivation and Validation
Development and Validation of a Novel Pediatric Appendicitis Risk Calculator (pARC)
Pediatrics Apr 2018, 141 (4) e20172699, PubMed ID: 29535251

Surgery: Appendicitis: Time to Appendectomy and Risk of Complicated Appendicitis
Time to Appendectomy and Risk of Complicated Appendicitis and Adverse Outcomes in Children.
JAMA Pediatr. 2017 Aug 1;171(8):740-746., PubMed ID: 28628705

Trauma: Abdominal Trauma: History and Physical Examination Accuracy
Accuracy of the Abdominal Examination for Identifying Children with Blunt Intra-Abdominal Injuries
J Pediatr. 2014 Dec;165(6):1230-1235.e5. PubMed ID: 25266346

Trauma: Head Trauma: ICU Admission Decision Rule (PECARN)
Development and Internal Validation of a Clinical Risk Score for Treating Children with Mild Head Trauma and Intracranial Injury
JAMA Pediatr. 2017 Apr 1;171(4):342-349., PubMed ID: 28192567

Trauma: Head Trauma: Point of Care Ultrasound for Skull Fractures
Point-of-Care Ultrasound for the Diagnosis of Skull Fractures in Children Younger Than Two Years of Age.
J Pediatr. 2018 May;196:230-236.e2., PubMed ID: 29499992

PEMCAR AUTHORS

Joanne Agnant, M.D.
Marc Auerbach, M.D., MSc.
Seema Awatramani, M.D.
Mariju Baluyot, M.D.
Joshua Beiner, M.D.
Rebecca Burton, M.D.
Sarah Case, M.D.
Kevin Ching, M.D.
Jason Choi, M.D.
Kelly Cleary, M.D.
Jennifer Curran, M.D.
Svetlana Dani, M.D.
Carrie Danziger, M.D.
Jeffrey Dela Cruz, M.D.
Guillermo De Angulo, M.D.
Ellen Duncan, M.D., PhD
Inna Elikashvili, M.D,
Kelsey Fawcett, M.D.
Jeffrey Fine, M.D.
Jessica Foltin, M.D.
Karen Franco, M.D
Katherine Fullerton, M.D.
Nicole Gerber, M.D.
Karen Goodman, M.D.
Dennis Heon, M.D.
Jeffrey Hom, M.D.
Shweta Iyer, M.D.
David Kessler, M.D., MSc.
Katrina Knapp, D.O.
Janienne Kondrich, M.D.
Rachel Kowalsky, M.D., MPH
George Kristinsson, M.D.
Maria Lame, M.D.
Deborah Levine, M.D.
Adriana Manikian, M.D.
Michael Mojica, M.D.
Nisha Narayanan, M.D.
Alexis Pankow, M.D.
Laura Papadimitropoulos, M.D.
John Park, M.D.
Kari Posner, M.D.
Martin Pusic, M.D.
Lilia Reyes, M.D.
Cindy Roskind, M.D.
Juliette Quintero-Solivan, M.D.
Alvira Shah, M.D.
Vaishali Shah, M.D.
Daniel Silva, M.D.
Louis Spina, M.D.
Dana Suozzo, M.D.
Ee Tay, M.D.
Susan Torrey, M.D.
James Tsung, M.D.
Michael Tunik, M.D.
Ramona Warren, M.D., MPH
Eric Weinberg, M.D.
Ethan Wiener, M.D.
Sheri-Ann Wynter, M.D.

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ACKNOWLEDGMENT

About the Authors

The authors are faculty and fellows of the division of pediatric emergency medicine as at NYU School of Medicine Departments of Emergency Medicine and Pediatrics. The authors are listed at the beginning of each critical article that they wrote or mentored

About the Editor

Michael Mojica, MD is an associate professor and director of education for the Division of Pediatric Emergency Medicine, and was the director of the pediatric emergency medicine fellowship program for 25 years. His is a member of the Institute for Innovation in Medical Education at NYU School of Medicine and is involved in educating medical students, residents, fellows, faculty and nurses.

Dr. Mojica is the developer and editor of PEM CARS. These comprehensive, critical article reviews are distributed monthly to faculty and residents of the departments of Emergency Medicine and Pediatrics.

He is interested in teaching evidence based clinical practice, biostatistics and research design and in educating the next generation of teachers how to teach. He is interested in the use of high fidelity simulation for teaching resuscitation leadership and communication skills.

Produced by the Institute for Innovations in Medical Education

ADMINISTRATIVE & OTHER ISSUES

1. EMS: LMA vs ETI in Cardiac Arrest (Adult): NEJM 2018
2. EMS: Prehospital Airway Management: JAMA 2000
3. CT: Radiation Exposure and Cancer Risk: Lancet 2012
4. Education: Simulation Debriefing: JAMA Peds 2013

EMS:

LMA VS ETI IN CARDIAC ARREST (ADULTS)

In adult patients with an out-of-hospital cardiac arrest does advanced airway management with a supraglottic airway device when compared to endotracheal intubation result in good outcomes defined as a modified Rankin Scale of 0-3?

Ellen Duncan, MD, PhD, Jeffrey Fine, MD
February 2019

Benger JR, Kirby K, Black S, Brett SJ, Clout M, Lazaroo MJ, Nolan JP, Reeves BC, Robinson M, Scott LJ, Smartt H, South A, Stokes EA, Taylor J, Thomas M, Voss S, Wordsworth S, Rogers CA.

EFFECT OF A STRATEGY OF A SUPRAGLOTTIC AIRWAY DEVICE VS TRACHEAL INTUBATION DURING OUT-OF-HOSPITAL CARDIAC ARREST ON FUNCTIONAL OUTCOME: THE AIRWAYS-2 RANDOMIZED CLINICAL TRIAL

JAMA. 2018 Aug 28;320(8):779-791.
PubMed ID: 30167701

STUDY DEFINITIONS	
POPULATION	Inclusion: 1. Adults (> 18years) with non-traumatic, out-of-hospital cardiac arrest 2. Treated by trial paramedics who were the 1st or 2nd to arrive at the scene 3. Resuscitation was initiated and continued by paramedics Exclusion: 1. Advanced airway in place at trial paramedic arrival at scene 2. Resuscitation inappropriate: Royal College Liaison Committee Guidelines 3. Mouth opening less than 2 cm 4. Detained by prison services 5. Previously included in trial or enrolled in another prehospital trial Setting: Paramedics from 4 English EMS agencies, cover 40% of population, Enrollment: 6/2015-8/2017, Follow-up: Ended 2/18
INTERVENTION	Supraglottic airway device not requiring inflation (soft, non-inflatable cuff)
CONTROL	Direct laryngoscopy with tracheal intubation. (2-person technique using an intubating bougie recommended)
CO-INTERVENTIONS	Advanced airway device training: Didactic, hands-on, competency assessed Bag valve mask ventilation (basic airway) prior to advanced airway Paramedics were instructed to attempt their assigned advanced airway device twice before attempting a second device. However, they were allowed to use whichever device they thought was appropriate for the circumstances Confirmation with end-tidal CO_2 Other interventions as per International Standard Resuscitation Guidelines
OUTCOME	Primary Outcome: Modified Rankin Scale a hospital discharge or 30 days if remained hospitalized (0-3 = Good Outcome, 4-6 = Poor Outcome (See Appendix)) Secondary Outcomes: 1. Initial ventilation success. Defined as chest rise with 2 attempts 2. Loss of a previously established airway 3. Sequence of airway interventions delivered 4. Return of spontaneous circulation (ROSC) 5. Airway management in place when ROSC occurred or resuscitation discontinued 6. Regurgitation (stomach contents in the mouth) or aspiration (stomach contents below the vocal cords or in the endotracheal tube) 7. Chest compression fraction (CPR recorder) 8. Time to death
DESIGN	Interventional: Randomized Clinical Trial (Pragmatic, multicenter)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	No. Patients were not randomized. Yes. Paramedics were randomized using block randomization. Randomization was stratified by 1. EMS provider organization, 2. paramedic experience and 3. distance from ambulance base station to usual destination hospital.
Was randomization concealed?	Unclear. Randomization concealment was not explicitly stated. However, it does not appear that the paramedics had the ability to bias the randomization process.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Patients were similar in demographic data, cardiac arrest details and ongoing airway management when the paramedics arrived at the scene (Table 1). Patients were also similar in presenting rhythm, event witnessed by bystander or paramedic and bystander CPR (Table E1 in the supplementary materials). Characteristics of the paramedics in each group were not presented for comparison.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Paramedics could not be blinded to the advanced airway intervention they were assigned. However, it is unlikely that paramedic knowledge of the treatment group would influence the assessment of the primary outcome. Outcome assessors were blinded to the study group.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Follow up was until hospital discharge or until 30 days if the patient remained hospitalized. The primary outcome was available for 99.9% of patients.
Were patients analyzed in the groups to which they were randomized?	Yes. 4,410 enrolled patients were randomized to tracheal intubation and 4,886 to supraglottic airway device 9,289/9,296 (99.9%) of randomized patients were included in the primary outcome intention to treat analysis (Figure 1). An analysis based on the first airway device received was also presented. A per protocol analysis based on the number of patients that received the intended advanced airway intervention was not presented.
Was the trial stopped early?	No. The trial was not stopped early. The sample size determination indicated that 9,070 total patients were needed for a 2% difference in the primary outcome to be statistically significant. 8,896 were included in the assessment of the primary outcome.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 1,523 paramedics (LMA: 759, ETI: 764)
N = 9,296 patients (LMA: 4,886, ETI: 4,440)

DEVICE UTILIZATION

RANDOMIZED DEVICE	ADVANCED AIRWAY ATTEMPED	RANDOMIZED DEVICE USED
Supraglottic Device	84.8% (4,415/4,886)	96.4% (3,994/4,145)
Endotracheal Intubation	77.4% (3,413/4,410)	79.6% (2,718/3,413)

PRIMARY OUTCOME: MODIFIED RANK SCALE (PROPORTION: GOOD OUTCOME)

	LMA	ETI	aRD (95% CI)[1]	aOR (95% CI)[2]
Intention to Treat Analysis	6.4% (311/4,882)	6.8% (300/4,407)	-0.6% (-1.6, 0.4%)	0.92 (0.77, 1.09)
Including Non-Resuscitated Patients	2.7% (311/11,462)	2.8% (300/10,741)	-0.2% (-0.6, 0.3%)	0.96 (0.81, 1.14)
Received Advance Airway Management	3.9% (163/4,158)	2.6% (88/3,418)	1.4% (0.5, 2.2%)	1.57 (1.18, 2.07)
First Airway Device Received	4.2% (193/4,630)	2.0% (58/2,838)	2.1% (1.2, 2.9%)	2.06 (1.51, 2.81%)

1. aRD = Adjusted Risk Difference (= LMA – ETI)
2. aOR = Adjusted Odds Ratio (= LMA/ETI)
GREEN = Statistically Significant, RED = Not statistically Significant
(A 2% difference was considered clinically significant by the authors)

SECONDARY OUTCOMES				
	LMA	ETI	aRD (95% CI)[1]	aOR (95% CI)[2]
Ventilation Success	87.4% (4,255/4,868)	79.0% (3,473/4,397)	2.1% (1.2, 2.9%)	1.92 (1.66, 2.22)
Unintended Loss of Established Airway	10.6% (412/3,900)	5.0% (153/3,081)	5.9% (4.6, 7.2%)	2.29 (1.86, 2.82)
Return of Spontaneous Circulation	30.6% (1,495/4,880)	28.4% (1,249/4,404)	2.2% (0.3, 4.2%)	1.12 (1.02, 1.28)
Regurgitation (before, during or after)	26.1% (1,268/4,865)	24.5% (1,072/4,372)	1.4% (-0.6, 3.4%)	1.08 (0.96, 1.20)
Aspiration (before, during or after)	15.1% (729/4,824)	14.9% (647/4,337)	0.1% (-1.5, 1.8%)	1.01 (0.88, 1.16)
Median Time to Death	67 minutes (n=4,871)	63 minutes (n=4,440)	Not Provided	aHR 0.97 (0.93, 1.02)
Compression Fraction (Proportion (IQR))	86% (81, 91%) (n=34)	83% (74, 89%) (n=32)	Not Provided	Not Provided

1. aRD = Adjusted Risk Difference (= LMA – ETI)
2. aOR = Adjusted Odds Ratio (= LMA/ETI), aHR = Adjusted Hazzard Ratio(= LMA/ETI)
GREEN = Statistically Significant, RED = Not statistically Significant

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The confidence intervals for the adjusted risk differences and the adjusted odds ratios are presented above. Given the large sample size, they are fairly narrow

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Unclear, it is unclear if data from an English cohort of patients is generalizable to the U.S. adult population. 64% of the population was male and the median age was 73 years. Over 63% of patients had bystander CPR. This is higher than in the US (AHA 2016: 46%). Results may not be generalizable to a pediatric population in which out of hospital respiratory arrest is more common than cardiac arrest.
Were all patient important outcomes considered?	Yes. The modified Rankin Scale is based on the level of functional independence and is a relevant patient-oriented outcome. The mRS was dichotomized but the data for each score is presented in Table 2. 92% of the patients in the poor outcome group (4-6) had a score of 6 and 57% of the good outcome group (0-3) had a score of 0 or 1 so it appears that the dichotomization was justified. The secondary outcomes included measures of device success as well as clinical outcomes.
Are the likely treatment benefits worth the potential harm and costs?	There was no difference in the primary outcome. The supraglottic airway device is easier to learn and easier to place. More than 20% of the advanced airway attempts in the ETI group crossed over to the LMA group. The LMA group was statistically more like to achieve ventilation.

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CLINICAL BOTTOM LINE

BACKGROUND: There is a lack of data on what interventions in the prehospital setting improve outcomes. Randomized clinical trials are rare and most recommendations are based on evidence from observational studies. Traditionally, direct laryngoscopy with tracheal intubation has been the advance airway technique most often recommended in prehospital cardiac arrest. However, endotracheal intubation requires extensive training, and is performed infrequently by paramedics. Intubation success is low and complications such as esophageal intubation are common. In contrast, the laryngeal mask airway is simple and faster to perform.

CLINICAL QUESTION: In adult patients with an out-of-hospital cardiac arrest does advanced airway management with a supraglottic airway device when compared to endotracheal intubation result in good outcomes defined as a modified Rankin Scale of 0-3?

DESIGN/VALIDITY: This was a well-designed, randomized clinical trial involving 1,532 paramedics representing 4 large EMS agencies in England that cover 40% of the population. Patients were included if they underwent a non-traumatic out-of-hospital cardiac arrest, were treated by trial paramedics who were the 1st or 2nd to arrive at the scene and if resuscitation was initiated and continued by EMS. Paramedics were randomized to use a supraglottic airway device not requiring inflation or two-person direct laryngoscopy with tracheal intubation utilizing an intubating bougie. Paramedics were trained in the device use and were required to demonstrate competency with the device. The paramedics could not be blinded to the study intervention though outcome assessors were blinded to the study group. Non-study co-interventions were guided by international resuscitation guidelines. The primary outcome was the modified Rankin Scale (MRS) a hospital discharge or 30 days if they remained hospitalized. An MRS score of 0-3 considered a good outcome and 4-6 considered a poor outcome. A number of device-related and patient outcomes were included as secondary outcomes. Patients were similar in demographic data, cardiac arrest details, ongoing airway management when the paramedics arrived at the scene, presenting rhythm, event witnessed by bystander or paramedic and bystander CPR. Data was available for 99.9% of patients for the primary outcome.

PRIMARY RESULTS: 1,523 paramedics caring for 9,296 patients were included in the trial. Paramedics randomized to the supraglottic airway device were more likely to utilize an advanced airway device when compared to those randomized to endotracheal intubation (LMA: 84.8% v ETI: 77.4%). In addition, the supraglottic airway device group was more likely to utilize the device they were randomized to (LMA: 96.4% vs ETI: 79.6%). Use of the supraglottic airway device was statistically more likely to achieve successful ventilation within two attempts (LMA: 87.4%, ETI: 79%, Adjusted risk difference: 2.1%, 95% CI (1.2, 2.9%) but was statistically more likely to have an unintended loss of an established airway (LMA: 10.6%, ETI: 5%, Adjusted risk difference: 5.9%, 95% CI (4.6, 7.2%)).

There was no statistically significant difference in the intention to treat analysis of the rate of a good outcome (MRS = 0-3) comparing the two study groups (LMA: 6.8%, ETI 6.4%, Adjusted risk difference: -0.6% 95% CI (-1.6, 0.4%). The authors considered a 2.0% difference in the proportion with a good outcome to be clinically significant. In an analysis based on initial advance airway device received, there was a statistically significant benefit of a good outcome in the supraglottic airway group (LMA: 4.2%, ETI: 2.0%, Adjust risk difference: 2.1%, 95% CI (1.2, 2.9%). This difference meets the authors criteria for clinical significance (2.0%). A per protocol analysis based on the ultimate intervention received was not presented.

There were no statistically significant differences in any of the subgroup or sensitivity analyses of the primary outcome (Figure 3). Those in the supraglottic airway device group had a significantly higher rate of return of spontaneous circulation (LMA: 30.6%, ETI 28.4%, Adjusted risk difference: 2.2% (0.3, 4.2%)). There was no difference in the rate declared dead at the scene or survived until ICU admission. There was no statistically significant difference in the median time to death, survival at 72 hours, regurgitation, aspiration or compression fraction between the two study groups.

APPLICABILITY: It is unclear if data from a English cohort of patients with out-of-hospital cardiac arrest is generalizable to the U.S. adult population. Bystander CPR has been demonstrated to improve outcomes. 63% of patients had bystander CPR before paramedic arrival. The rate of bystander CPR in the US is approximately 46% (AHA 2016). Results may not be generalizable to a pediatric population in which respiratory arrest is more common the cardiac arrest. This is particularly true of respiratory arrest due to upper airway obstruction (e.g. croup, smoke inhalation and anaphylaxis) in which a supraglottic airway is unlikely to provide effective ventilation.

AUTHOR'S CONCLUSION: "In adult patients with an out-of-hospital cardiac arrest does advanced airway management with a supraglottic airway device when compared to endotracheal intubation result in good outcomes defined as a modified Rankin Scale of 0-3?"

POTENTIAL IMPACT: The supraglottic airway device is easier to learn and easier to insert. More than 20% of the advanced airway attempts in the ETI group crossed over to the LMA group. The LMA group was statistically more like to achieve ventilation but more likely to result in loss of an established airway. However, changing to an all LMA approach to advanced airway management in the pre-hospital setting would further limit paramedic experience with endotracheal intubation for those circumstances when bag-valve-mask ventilation and a supraglottic airway are insufficient such as upper airway obstruction.

MODIFIED RANKIN SCALE		
0	No symptoms at all	
1	No significant disability despite symptoms	Able to carry out all usual duties and activities
2	Slight disability	Unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability	Requiring some help, but able to walk without assistance
4	Moderately severe disability	Unable to walk and attend to bodily needs without assistance
5	Severe disability	Bedridden, incontinent and requiring constant nursing care and attention
6	Dead	

WEBLINK: MD Calc: Modified Rankin Scale
WEBLINK: Joint Commission Quality Measures

EMS:
PREHOSPITAL PEDIATRIC AIRWAY MANAGEMENT

In pediatric patients requiring prehospital airway management by paramedics does endotracheal intubation when compared to bag-valve-mask ventilation improve overall survival to hospital discharge and survival with good neurologic outcome?

Michael Mojica, M.D.
June 2017

Gausche M, Lewis RJ, Stratton SJ, Haynes BE, Gunter CS, Goodrich SM, Poore PD, McCollough MD, Henderson DP, Pratt FD, Seidel JS.

EFFECT OF OUT-OF-HOSPITAL PEDIATRIC ENDOTRACHEAL INTUBATION ON SURVIVAL AND NEUROLOGICAL OUTCOME: A CONTROLLED CLINICAL TRIAL

JAMA. 2000 Feb 9;283(6):783-90.,
PubMed ID: 10683058

STUDY DEFINITIONS	
POPULATION	Paramedics: 2,584 paramedics from 56 provider agencies, two-tiered system (BLS and ALS). Prior adult endotracheal intubation training 3-hour course consisting of: lectures, skill demonstration and skills teaching. Must have demonstrated appropriate attainment of skills. Skills included: 1. Sizing and placement of oral and nasopharyngeal airways 2. Use of a length based resuscitation tape for equipment selection 3. Endotracheal Intubation 4. Bag-valve-mask ventilation using the “squeeze, release, release” technique at a rate of ≤ 30 breaths/minute (< 1 year) or ≤ 20 breaths/minute (≥ 1 year) 5. Pediatric Magill forceps use for foreign body removal 6. CO_2 detector as an adjunct to assess correct endotracheal tube placement Patients: ≤12 years or estimated weight < 40 kg Required airway management based on ≥ 1 of the following: 1. Cardiopulmonary arrest: Apneic without a pulse 2. Respiratory arrest: Apneic with a pulse 3. Respiratory failure: Respiratory rates > 60/min or < 12/min with a non-purposeful response to pain or no response to pain 4. Complete or severe partial airway obstruction 5. Traumatic cardiopulmonary arrest 6. Traumatic respiratory arrest 7. Closed or open head trauma with non-purposeful or no response to pain 8. Paramedic assessment that assisted ventilation was necessary. Etiology Subgroups (See Appendix) Setting: Two contiguous counties with population > 12 million, 3/1994-1/1997
INTERVENTION	Endotracheal intubation (Even days) Use of Magill forceps for foreign body removal if BLS maneuvers unsuccessful
CONTROL	Bag-valve-mask ventilation (Odd days) Use of Magill forceps for foreign body removal if BLS maneuvers unsuccessful
CO-INTERVENTION	Standardized data collection form completed by paramedic and ED provider. Structured phone interview with paramedic immediately after transfer of care. Retrospective review by study investigators of: inpatient records, transfer records, coroner’s reports, and EMS report forms.
OUTCOME	Primary Outcome: Survival to discharge from the final, acute care hospital Secondary Outcome: Neurological status at discharge Categories from the Modified Pediatric Cerebral Performance Category Scale (“Good neurologic outcome” defined as 1 or 2) 1. Normal or no change from baseline 2. Mild disability 3. Moderate disability 4. Severe disability 5. Coma or vegetative state 6. Death Endotracheal Intubation Attempt (ETI): Placement of a laryngoscope in patient’s mouth with the intent of intubation, regardless of whether an endotracheal tube was passed into the oropharynx or trachea. Successful Intubation: Placement of endotracheal tube into a trachea or mainstem bronchus Complications Specific to ETI: Main stem intubation, recognized dislodgment, unrecognized dislodgment, esophageal intubation
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS	
Were patients randomized?	Yes. A “pseudo” randomization scheme was used based on odd and even days.
Was randomization concealed?	No. Randomization was not concealed. BVM was performed initially in 95% of patients in the BVM group. Endotracheal intubation was attempted initially in 77% of the ETI group. It is unclear why the primary interventions were not selected, particularly in the ETI group
Were patients in the study groups similar with respect to known prognostic factors?	Yes. See Table 1. Age, ethnicity, sex, proportion declared dead without resuscitation in the ED and etiology of illness or injury were similar in the two study groups.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study was not blinded. However, the lack of blinding in the study should not affect the interpretation of the survival outcomes.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Follow up was until discharge from the final, acute care hospital.
Were patients analyzed in the groups to which they were randomized?	Yes. The primary analysis was based on the intention to treat principle. A per protocol analysis was also performed and the two analyses differed significantly. The authors point out the importance of an intention to treat analysis because intubation success is not independent of prognosis. For example, Intubation success may be increased in patients in cardiac arrest who are most likely to die.
Was the trial stopped early?	No. The trial was not stopped early though multiple interim analyses took place.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 830, ETI: 420, BVM: 410
Median age: 1.2 years (73% < 3 years)

PROCEDURE PERFORMED		
	BVM GROUP (410)	ETI GROUP (420)
BVM ONLY	391 (95%)	115 (27%)
BVM AFTER FAILED ETI	9 (2%)	128 (30%)
ETI ONLY	10 (2%)	177* (47%)
*3/177 with Esophageal Intubation		

INTUBATION SUCCESS BY GROUP	
ETI Group	177/305 (57.0%)
BVM Group	10/19 (52.6%)
TOTAL	187/324 (57.7%)

INTUBATION SUCCESS BY AGE (ETI GROUP)	
< 3 years	127/225 (56%)
3-8 years	34/56 (61%)
> 8 years	16/24 (67%)
All Ages (p = NS)	177/305 (58%)

SURVIVAL: OVERALL		
	Intention to Treat	Per Protocol
BVM	123/404 (30%)	208/635 (33%)
ETI	110/416 (26%)	25/185 (14%)
ARD*	4% (-2.2, 10%)	19.2% (12.6, 24.9%)
*Absolute Risk Difference (95% CI)		

SURVIVAL: GOOD NEUROLOGIC OUTCOME		
	Intention to Treat	Per Protocol
BVM	92/404 (23%)	162/635 (33%)
ETI	85/416 (20%)	15/185 (8%)
ARD*	2.3% (-3.3, 8%)	17.4% (11.6, 22.1%)
*Absolute Risk Difference (95% CI)		

SUBGROUP ANALYSIS: BASED ON ETIOLOGY

Significantly worse survival with ETI in patients with respiratory arrest and child maltreatment as an etiology. Significantly worse neurologic outcome with ETI in patients with foreign body aspiration as an etiology.

OUT OF HOSPITAL CARE TIME (MEDIAN (IQR))			
	BVM	ETI	P
Scene Time (min)	9 (5-13)	11 (7-16)	< 0.001
Total Time (min)	20 (16-26)	23 (18-29	< 0.001
No difference in Arrival or Transport times			

INTUBATIONS THOUGHT SUCCESSFUL (186)*	
Unrecognized Dislodgement	12 (6%)
Recognized Dislodgement	15 (8%)
Esophageal Intubation	3 (2%)
Mainstem Intubation	33 (18%
Incorrect Tube Size	44 (24%)
TOTAL	107 (58%)
*ETI and BVM groups combined	

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?
Confidence intervals for the absolute risk difference are provided above and are fairly narrow. Confidence for other comparisons were not provided.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. The two counties had a population of over 12 million so that a wide variety of patients were included. Some of the subcategories of etiology such a submersion injury are less likely in our NYC population. However, submersion injury was not one of the subgroup etiologies that were associated with worsening survival or neurologic outcome in the ETI group (respiratory arrest, child maltreatment and foreign body aspiration).
Were all patient important outcomes considered?	Yes. All important outcomes were reported. Today, continuous quantitative CO_2 monitoring could be used to assess the adequacy of ventilation.
Are the likely treatment benefits worth the potential harm and costs?	BVM was as successful as ETI in terms of survival. BVM was completed successfully a high proportion of the time and is not associated with the ETI complications. Training time for ETI could possibly be allocated to other essential pediatric skills. However, ETI skills would still be required in those with upper airway obstruction (e.g. croup, smoke inhalation, anaphylaxis).

CLINICAL BOTTOM LINE

BACKGROUND: Bag-valve-mask ventilation (BVM) is an essential skill and provides effective ventilation in most pediatric patients with the exception of patients with upper airway obstruction. Endotracheal intubation (ETI) can provide a more definitive airway and can provide an alternative route for medication delivery. Endotracheal intubation requires more training and it is a skill that is difficult to maintain in a pediatric population where it is not performed frequently. Skill and experience in adult endotracheal intubation is not necessarily transferable to pediatric endotracheal intubation.

CLINICAL QUESTION: In pediatric patients requiring out of hospital airway management does endotracheal intubation when compared to bag-valve-mask ventilation by paramedics improve overall survival to hospital discharge and survival with good neurologic outcome?

DESIGN/VALIDITY: This was a well-designed clinical trial of endotracheal intubation compared to bag-valve mask ventilation by paramedics in children requiring airway management. 830 patients (ETI: 420, BVM: 410) were included in the trial's primary intention to treat analysis. "Good neurologic outcome" defined as normal, no change from baseline or mild disability.

The trial was "pseudo" randomized by odd and even days. Blinding was not possible but lack of blinding would not affect the assessment of the survival outcomes. Clear definitions were utilized and multiple methods were used to collect trial data.

PRIMARY RESULTS: Bag-valve mask ventilation was successfully performed in 97% of the patients in the BVM group. The remaining 2% were endotracheally intubated but it is unclear if that was due to unsuccessful bag-valve-mask ventilation. In contrast, 57% of the patients in the endotracheal intubation group were successfully intubated. Intubation success was higher in those greater than 8 years of age but the difference was not statistically significant. Adequacy of ventilation was assessed as "good" by paramedic report (BVM: 83%, ETI: 82%, $p = 0.62$) and by pulse oximetry in a subset of patients with a pulse (BVM: 98%, ETI: 97%, $p = 0.29$).

There was no statistically significant difference in overall survival or survival with a good neurologic outcome between the BVM group and ETI group in the primary intention to treat analyses. In the subgroup analysis based on etiology there was significantly worse survival in ETI patients with respiratory arrest and child maltreatment and significantly worse neurologic outcome in ETI patients with foreign body aspiration.

The ETI group had a statistically significant lower rate of overall survival and survival with a good neurologic outcome in the per protocol analyses. The authors point out the importance of an intention to treat analysis because intubation success is not independent of prognosis. Intubation success may be increased in patients in cardiac arrest who are most likely to die. Time at the scene (1-minute difference) and overall time (2-minute difference) was statistically higher in the ETI group though the clinical importance of these difference is unclear.

There was no statistically significant difference between the two groups in the complications of vomiting, aspiration, gastric distension and oral or airway trauma. There was a higher rate of gastric distension in the BVM group (31%) compared to the ETI group (7%) though this was not statistically significant. There was no difference in hospital length of stay or days of ICU stay.

There was a high rate of complications (58%) including potentially life-threatening complications such as esophageal intubation (2%) and unrecognized dislodgement (6%) in patients thought to be successfully intubated. This rate may be underestimated. Other complications include: recognized dislodgment (8%), mainstem intubation (18%) and incorrect endotracheal tube size (24%)

SURVIVAL				
	OVERALL SURVIVAL		GOOD NEUROLOGIC OUTCOME	
	Intention to Treat	Per Protocol	Intention to Treat	Per Protocol
BVM	123/404 (30%)	208/635 (33%)	92/404 (23%)	162/635 (33%)
ETI	110/416 (26%)	25/185 (14%)	85/416 (20%)	15/185 (8%)
ARD*	4% (-2.2, 10%)	19.2% (12.6, 24.9%)	2.3 (-3.3, 8%)	17.4% (11.6, 22.1%)
*Absolute Risk Difference (95% CI)				

APPLICABILITY: The inclusion of patients from two counties with a population of over 12 million and the inclusion of 2,584 paramedics from 56 provider agencies likely makes the study's results generalizable to most paramedics in urban, rapid transport systems. Applicability to rural transport systems is unclear. The success and complication rate for endotracheal intubation may vary with paramedics with different training or experience with pediatric endotracheal intubation.

AUTHOR'S CONCLUSION: "The addition of pediatric endotracheal intubation to the paramedic scope of practice, compared with bag-valve-mask alone, does not improve survival or neurological outcome. For endotracheal intubation in this setting, scene time was prolonged and fatal complications were frequent. These results call into question the current practice of paramedics intubating children in an urban, out-of-hospital setting, as well as the rationale of allowing less- experienced personnel, such as basic emergency medical technicians to intubate children. Emergency medical services systems should focus on training its providers to perform effective bag-valve-mask, coupled with expeditious transport, and defer pediatric endotracheal intubation until the patient arrives in the emergency department."

POTENTIAL IMPACT: ETI intubation when compared to bag-valve-mask ventilation was not associated with improved overall or neurologically favorable survival. It did result in significantly longer scene times. It was successful only approximately 58% of the time and associated with a high rate of complications when thought to be successful. Unlike endotracheal intubation, bag-valve mask ventilation is an easier skill to both learn and maintain and experience with adults is more easily translatable to children. It may be more prudent for EMS systems to focus of pediatric bag-valve mask ventilation and rapid transit to the emergency department.

The Fire Department of New York Bureau of Emergency Medical Services (FDNY-EMS) is the largest centrally administered EMS service in the country. The 2014 advanced emergency medical technician (paramedic) protocols for pediatric non-traumatic cardiac arrest include the following recommendation: "perform advanced airway management if less invasive methods of airway management are not effective".

A recent observational study using an out of hospital pediatric arrest registry in Japan including 2,157 patients (BVM: 1,792, Advanced Airway management: 365) demonstrated similar results. There was no significant difference is neurologically favorable survival when BVM was compared to advanced airway management after adjusting for potential confounders (Ohashi-Fukuda, Resuscitation 2017, PubMed ID: 28267617).

There remain a number of unanswered questions. Would endotracheal intubation improve survival if it was successful more frequently and not associated with a high complication rate? Should effort be put into repetitive training to maintain skills for a procedure that occurs infrequently in children? Would use of laryngeal mask airways in the pre-hospital setting provide better ventilation of pediatric patients with ease of use intermediate between bag-valve-mask ventilation and endotracheal intubation and without many of the life-threatening complications associated with endotracheal intubation?

APPENDIX: SUBGROUPS

ETIOLOGY SUBGROUPS*
Sudden infant death syndrome
Submersion injury
Head injury
Multiple trauma
Foreign body aspiration
Seizure
Child maltreatment
Cardiopulmonary arrest
Respiratory arrest
Reactive airway disease.
*Apparent to out-of-hospital providers and by review of the final medical record.

CT IMAGING:
RADIATION EXPOSURE AND CANCER RISK

In pediatric patients without a history of cancer who are undergoing CT scanning do patients receiving a high radiation dose when compared to those receiving a low radiation dose have an increased risk of developing nervous system tumors or leukemia?

Alvira Shah, M.D., Michael Mojica, M.D.
July 2012

Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, Howe NL, Ronckers CM, Rajaraman P, Sir Craft AW, Parker L, Berrington de González A.

RADIATION EXPOSURE FROM CT SCANS IN CHILDHOOD AND SUBSEQUENT RISK OF LEUKEMIA AND BRAIN TUMORS: A RETROSPECTIVE COHORT STUDY.

Lancet. 2012 Aug 4;380(9840):499-505.,
PubMed ID: 22681860

STUDY DEFINITIONS	
POPULATION	Inclusion: < 22 years without malignant disease Exclusion: Exit date < 2 years for leukemia or < 5 years for brain tumors after the first scan to reduce possibility that CT scans were for suspected cancer. Patients who could not be traced by NHSCR, had missing information, inaccurate information on date of CT scan. Setting: CT between 1985 and 2002 at 81 National Health Service (NHS) regional hospitals in Great Britain.
EXPOSURE	Risk of leukemia in those who received > 30 mGy of CT radiation Risk of CNS Tumor in those who received > 50 mGy of CT radiation
NO EXPOSURE	Risk of leukemia or CNS tumor in those who received < 5 mGy of CT radiation
OUTCOME	Relative risk of leukemia or central nervous system tumor
DESIGN	Observational study: Retrospective cohort study
DEFINITIONS	Data included: body parts examined by CT, cancer incidence, mortality and loss-to-follow-up. Estimated radiation absorbed doses in the appropriate organ (red bone marrow or brain) for each type of scan Leukemia Subgroups: Acute lymphoblastic leukemia, acute myeloid leukemia, myelodysplastic syndromes, and leukemia excluding myelodysplastic syndrome Malignant and Benign Brain Tumors: World Health Organization's International Classification of Diseases for Oncology (spinal tumors were excluded).

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
Aside from the exposure of interest did the exposed and control groups start and finish with the same risk for the outcome?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or did statistical adjustments address the imbalance).	Unclear. There is very limited data on the cohort studied other than the age, no previous cancer diagnosis, and had CT scans in National Health Service centers in Great Britain between 1985-2002. There is no comparison of potential prognostic factors or indications for imaging. For example, patients with trisomy 21 or neurofibromatosis would be at higher risk for leukemia and brain tumors respectively and would need to be equally distributed or statistically corrected for.
Were the circumstances and methods for detecting the outcome similar?	Yes. The method to obtain information was from the National Health Service Central Registry (NHSCR). As for the circumstances, the indications for CT scans were not available.
Was follow-up sufficiently complete?	Unclear. Patients who could not be traced were excluded. Characteristics of those excluded were similar to those included.

WHAT ARE THE RESULTS?

How strong is the association between exposure and outcome?

Primary Outcome: Relative Risk of leukemia, CNS tumor

RR (Leukemia) = (risk > 30mGy)/(risk < 5mGy) = 3.18

RR (CNS tumor)=(risk > 50-74mGy)/(risk < 5mGy) = 2.82
Mean dose numerator: 60.4 mGy

RR(CNS tumor) = (risk > 50 mGy)/(risk < 5mGy) = 3.32
Mean dose numerator: 104.1 mGy

Absolute Risk(Leukemia) = 74/178,604 = 0.0004 = 0.04%
= 4/10,000 = 1/2,500

Absolute Risk(CNS tumor) =135/176,587=0.0008= 0.08%
= 8/10,000 = 1/1,250

Figure1: A linear, statistically significant dose response relationship was seen for both leukemia and CNS tumors

The denominator for the relative risk calculation were those who received less than 5 mGy radiation, and not those who did not have exposure to imaging radiation. This could potentially underestimate the risk of cancer.

How precise is the estimate of the risk?

RR (Leukemia): 3.18, 95% CI (1.46, 6.94)
RR (CNS tumor 50-74): 2.82, 95% CI (1.33, 6.03)
RR (CNS tumor > 50: 3.32, 95% CI (1.84, 6.42)

The confidence intervals are wide because there are few cases of cancer. The confidence intervals do not include 1 indicating a statistically significant increase in risk in those exposed to higher doses of radiation

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Unclear. We only know that the patients were less than 22 years of age, from Great Britain, and > 80% were white. We do not know what other risk factors they may have had, or what the indications for imaging were.
Was follow-up sufficiently long?	Unclear. Patients who received CT from 1985 – 2002 were included. The follow-up on cancer incidence and mortality was from 1/1/85 – 12/31/08. Data collection continued until: the date of 1st cancer diagnosis, death; loss to follow-up or Dec 31, 2008. The mean duration of follow-up was 10 years with a minimum of 6 years and a maximum of 26 years. However, it is not certain for how long after radiation exposure one is susceptible to developing cancer and later developing cancers may have been missed.
Is the exposure similar to what might occur in my patient?	Unclear. The scans occurred between 1985 and 2002. Radiation doses may have been higher than those used today using the ALARA (As Low As Reasonable Achievable) principle.
What is the magnitude of the risk?	The study provides the following magnitude measures (assuming typical doses for scans done after 2001) <u>Children < 15 years old</u> 2-3 head CTs (~60 mGy) triples the risk of brain tumors 5-10 head CTs (~50 mGy) triples risk of leukemia. Lifetime excess risk: 1 cancer/1,000 head CTs < 5 years Lifetime excess risk: 1 cancer/2,000 head CTs = 15 years Lifetime excess risk: 1 cancer/500 abdominal/pelvis CT (regardless of the age of exposure)
Are there any benefits that offset the risks associated with exposure?	There are definite benefits to CT use. Particularly in situations where a timely diagnosis and treatment are needed. To best utilize CT, the benefits of what the CT will reveal should outweigh the harms of radiation. In this study, we do know the indications for CT, if it was beneficial or if alternative imaging options were available.

CLINICAL BOTTOM LINE

BACKGROUND: The risk of developing cancer after radiation exposure has previously been extrapolated from data on nuclear weapons use or nuclear plant melt down. Children are known to be more radiosensitive. This large retrospective cohort study is the first to directly measure the risk of cancer in children after exposure to imaging (CT) radiation.

CLINICAL QUESTION: In pediatric patients without a history of cancer who are undergoing CT scanning do patients receiving a high radiation dose when compared to those receiving a low radiation dose have an increased risk of developing central nervous system tumors or leukemia?

DESIGN/RISK OF BIAS: This was a very well designed study that may have benefitted from a better description of the patient population to improve generalizability.

PRIMARY RESULTS: This study demonstrated that the use of CT scans in children to deliver cumulative doses of about 50 mGy might triple the risk of leukemia and doses of about 60 mGy might triple the risk of brain cancer. A dose response relationship and a leukemia risk similar to Japanese studies add weight to these conclusions. Because these cancers are relatively rare, the absolute risks remain small. The authors estimate a lifetime excess risk of 1 cancer per 1,000 head CTs in patients less than 5 years old and a lifetime excess risk is 1 cancer per 2,000 head CTs at 15 years old.

APPLICABILITY: Limited data were provided on the patients included. We only know the patients were less than 22 years of age, from Great Britain, and > 80% were white. We do not know what other risk factors they may have had, and what were the indications for imaging. It is difficult to assess the harms of imaging without the context of its benefits.

AUTHOR'S CONCLUSION: "Use of CT scans in children to deliver cumulative doses of about 50 mGy might almost triple the risk of leukemia and doses of about 60 mGy might triple the risk of brain cancer. Because these cancers are relatively rare, the cumulative absolute risks are small: in the 10 years after the first scan for patients younger than 10 years, one excess case of leukemia and one excess case of brain tumor per 10 000 head CT scans is estimated to occur. Nevertheless, although clinical benefits should outweigh the small absolute risks, radiation doses from CT scans ought to be kept as low as possible and alternative procedures, which do not involve ionizing radiation, should be considered if appropriate."

POTENTIAL IMPACT: The clinical benefits of CT should outweigh the small absolute risks of cancer. Radiation doses from CT's should be calibrated specifically to pediatric patients and kept as low as reasonably achievable (ALARA). Alternative modalities without ionizing radiation such as ultrasound or MRI should be utilized whenever possible.

RESUSCITATION EDUCATION: SIMULATION DEBRIEFING

Does the use of a scripted debriefing tool for a resuscitation scenario by novice instructors when compared to unscripted debriefing, improve team clinical performance, team leader behavioral performance and individual student knowledge?

Alexis Pankow, M.D., Lilia Reyes, M.D.
January 2014

Cheng A, Hunt EA, Donoghue A, Nelson-McMillan K, Nishisaki A, Leflore J, Eppich W, Moyer M, Brett-Fleegler M, Kleinman M, Anderson J, Adler M, Braga M, Kost S, Stryjewski G, Min S, Podraza J, Lopreiato J, Hamilton MF, Stone K, Reid J, Hopkins J, Manos J, Duff J, Richard M, Nadkarni VM;
EXPRESS Investigators.

EXAMINING PEDIATRIC RESUSCITATION EDUCATION USING SIMULATION AND SCRIPTED DEBRIEFING; A MULTICENTER RANDOMIZED TRIAL

JAMA Pediatr. 2013 Jun;167(6):528-36,
PubMed ID: 23608924

STUDY DEFINITIONS	
POPULATION	Novice Instructors: 1. Residents (pediatric, emergency medicine, pediatric subspecialty) ≥ PGY3 2. Respiratory therapists. paramedics with > 5 years clinical experience. PALS certification within 2 years. Inter-Professional Health Care Teams: 1-2 pediatric nurses, 2 physicians (residents/fellows in pediatrics, anesthesia, family medicine, emergency medicine, pediatric emergency medicine, pediatric critical care, pediatric anesthesia), and/or 1 pediatric respiratory therapist or transport paramedic. Exclusion: Experienced instructors: ≥ 3 courses for healthcare professionals where simulation was followed by debriefing Setting: 14 Pediatric Tertiary Care Centers in North America: The Examining Pediatric Resuscitation Education Using Simulation and Scripted Debriefing (EXPRESS) network. 7/2008-2/2011
INTERVENTION	1. A debriefing script focused on existing PALS learning objectives. To guide conversation between novice debriefers and trainees, promote reflective learning (See Appendix) 2. High physical-realism simulator “turned on” including vital sign monitoring, audio feedback, breath sounds, chest rise, heart sounds, and palpable pulses.
CONTROL	1. Standard debriefing without a script 2. Low Physical Realism simulator: Use of high physical-realism simulator with compressor “turned off” eliminating physical examination findings.
STUDY GROUPS	1. Non-scripted debriefing AND Low physical-realism simulator. 2. Scripted debriefing AND Low physical-realism simulator. 3. Non-scripted debriefing AND High physical-realism simulator. 4. Scripted debriefing AND High physical-realism simulator.
OUTCOME	Post-intervention vs Pre-intervention: Percentage difference (0%-100%) 1. Individual team member knowledge: Multiple choice question test (MCQ) 2. Team leader performance: Behavioral Assessment Tool (BAT) 3. Team performance: Clinical Performance Tool (CPT)
DESIGN	Prospective, Blinded, Randomized Clinical Trial, Factorial design

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. The participants were randomized into one of 4 arms of the study groups using block randomization from a web-based generator. There were 2 different multiple choice question sequences for pre and post testing and the sequence of scenarios also varied. The instructors were randomized into scripted versus unscripted debriefing.
Was randomization concealed?	Yes. Concealment was done for the participants by placing the contents of each arm assignment in opaque envelopes.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. See Table 1 and Table 2. Characteristics of the novice debriefers and the team participants were similar in the 4 study groups. The study accounted for varying levels of knowledge and experience by assessing pre and post intervention multiple choice questionnaires so that each person was compared to their own pre-intervention score (i.e. a paired analysis).
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The reviewers of the video were blinded to the assignment of the group as both the scripted and unscripted instructors carried a clipboard with contents not visible to the reviewer. The low versus high fidelity simulation was not blinded as it is clear whether the manikin was in the high-fidelity mode.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	443/453 (98%) participants, 104/104 (100%) teams included in MCQ test analysis 387/453 (85%) participants, 90/104 (86%) teams included in the BAT and CPT analysis 37 participants, 8 teams randomly removed for validation 29 participants, 6 teams excluded for poor audio or video
Were patients analyzed in the groups to which they were randomized?	Yes. This was both an intention to treat and a per protocol analysis.
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

How large was the treatment effect?

387 Participants (90 teams)
1. Non-scripted, low-realism: 97 participants (23 teams)
2. Scripted, low-realism: 93 participants (22 teams)
3. Non-scripted high-realism: 103 participants (23 teams)
4. Scripted, high-realism: 94 participants (22 teams)

43% Physicians: 53% PGY1-2, 24% PGY3, > PGY3 23%
45% Nurses: Average 10 years experience
73% PALS within 2 year

90 Novice Instructors: 72% physician, 21% nurse
(87% of physicians were PGY4, PGY5 or fellows)

SCRIPTED VS NON-SCRIPTED DEBRIEFING

MULTIPLE CHOICE QUESTION TEST (MCQ): KNOWLEDGE			
	Scripted	Not Scripted	P Value
Pre	69.3%	69.1%	0.87
Post	74.6%	72.6%	0.09
Change	(+) 5.3%	(+) 3.6%	0.04*

*While statistically significant a difference in improvement in score of 1.7% (5.3-3.6%) is likely not clinically significant.

BEHAVIORAL ASSESSMENT TOOL (BAT): TEAM LEADER			
	Scripted	Not Scripted	P Value
Pre	52%	54%	0.99
Post	82%	74.6%	0.24
Change	(+) 16%	(+) 8%	0.03*

*While the 8% difference in BAT is statistically significant the authors did not report what they considered clinically significant.

TEAM CLINICAL PERFORMANCE (CPT): TEAM			
	Scripted	Not Scripted	P Value
Pre	73%	74.6%	0.95
Post	82.5%	82.5%	0.38
Change	(+) 7.9%	(+) 6.7%	0.18

HIGH VERSUS LOW FIDELITY SIMULATION
No significant differences between the groups for MCQ, BAT or CPT scores.

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?
Confidence intervals for the difference between the change in scores were not provided.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. The study participants were similar to the groups that we teach during our PALS courses and simulation sessions. Our faculty and fellows have more experience with simulation debriefing than the novice debriefers in the study.
Were all patient important outcomes considered?	Yes. However, no follow up was done to assess for persistence of the student's educational gains or the debriefers skills.
Are the likely treatment benefits worth the potential harm and costs?	No potential harm as both groups seem to have similar post intervention MCQ scores indicating that they have achieved the educational goals for the intervention. There should be minimal cost as well as a script could easily be distributed for PALS instructors to use.

CLINICAL BOTTOM LINE

BACKGROUND: Simulation has become an increasingly popular method to achieve a variety of learning objectives. This is particularly true of resuscitation, which requires both individual and team knowledge, skills and communications. It is vital to continue to examine how to best create the most effective educational experience. The optimal method to debrief resuscitation scenarios has not been determined.

CLINICAL QUESTION: Does the use of a scripted debriefing tool for a resuscitation scenario by novice instructors when compared to unscripted debriefing improve team clinical performance, team leader behavioral performance and individual student knowledge?

DESIGN/VALIDITY: This study was a well-designed randomized trial of two interventions: scripted versus unscripted debriefing and high versus low reality scenarios. The analysis included 443 participants in 104 teams in the multiple-choice question test analysis (team member knowledge) and 387 participants in 90 teams in the behavioral assessment tool analysis (team leader performance) and the clinical performance tool analysis (team performance). The design was limited by the inclusion of a single scenario and lack of measurement of retention of novice debriefers and team knowledge and skills.

PRIMARY RESULTS: This study demonstrated that scripted debriefings along with clear educational goals may be more effective at creating an optimal educational experience with novice instructors. There was a statistically significant increase in knowledge (1.7%) and team leader behavioral performance (8%) in the scripted debriefing group. The importance of these modest improvements is unclear. There was no statistically significant improvement in increase in team clinical performance.

High fidelity simulation showed no improved outcomes compared to low fidelity simulation though the use of high reality findings such as respiratory rate, breath sounds and pulses were not part of the cardiopulmonary arrest scenarios. The use of low fidelity simulators is more cost effective and can be used more widely.

APPLICABILITY: The inclusion of 14 study centers as well as a variety of novice debriefers and team members make it likely that the study's results are generalized to a variety of debriefers and team members. The study was limited to novice debriefers who had previously taught in less than 3 courses for healthcare professionals where simulation was followed by debriefing. The study's results on the efficacy of scripted debriefing may not be generalizable to debriefers with more experience. In addition, a scripted debriefing tool may not be adequate when team performance and communication deviates significantly from that expected. The study's conclusion that that there was no effect on performance for high or low realism simulations were based on a single scenario that did not rely on physical examination findings and may not be generalizable to other scenarios where physical examination cues from the manikin play a more essential role in decision making.

AUTHOR'S CONCLUSION: "Our study has demonstrated that scripted debriefing for simulation-based pediatric resuscitation education improves educational outcomes (knowledge) and behavioral performance of the team leader. Turning on or off physical realism features of the mannequin does not improve learning outcomes when other aspects of physical, conceptual, and emotional realism are maintained. Further work is needed to identify the impact of scripted debriefing when used by more experienced instructors, for longer debriefing sessions, and in the context of other types of simulated scenarios."

POTENTIAL IMPACT: A scripted debriefing tool may help to standardize debriefing by novices by providing both a structure for the debriefing session and a reminder of session goals. The American Heart Association has in recent years standardized the lectures given during the Pediatric Advanced Life Support Course by providing videos of recorded lectures and have developed guides to debriefing each scenario as well as guides to assessing team leader and team member performance. The applicability of scripted debriefing to other scenarios and an assessment of retention of team knowledge and skills would be helpful.

APPENDIX

SEQUENCE

1. Orientation to simulator
2. Baseline multiple choice question test
3. 1st simulation scenario
4. Debriefing (scripted vs non-scripted) by novice instructor
5. 2nd simulation scenario
6. Post-debriefing test.

SCENARIO

Standardized, 12-minute, Infant in hypotensive shock progressing to ventricular fibrillation. (1st and 2nd scenarios with two different stems, same clinical situation)

SCRIPT

- Developed by a multidisciplinary team: pediatric emergency, intensive care physicians, organizational behavior specialist, medical educator and human factors engineers.
- Iterative process. Based on advocacy-inquiry debriefing theory.
- Directed to use and follow the script as closely as possible. Given no further instructions.
- Non-scripted debriefing instructor asked to conduct a debriefing to cover the predefined learning objectives. Given no further instruction.

LINK: FULL DEBRIEFING SCRIPT (SUPPLEMENTARY MATERIALS)
(Scroll down to the STUDY PARTICIPANTS Section and Click on: EMETHODS.

DEBRIEFING SCRIPT OUTLINE INSTRUCTIONS	
1	You will have only 20 minutes to debrief.
2	Follow the script as closely as possible. Read directly from the script where items are italicized.
3	You have 3 debriefing “cards” to utilize a. Outline card: You are currently reading this card. It outlines the format of the script. b. Medical management card: Use this to discuss medical issues. c. Crisis resource management card: Use this to discuss teamwork and leadership issues.
4	The debriefing script has several phases, and each phase has an assigned time allocation. Try to stay on time.
5	The last phase: ‘Dealing with an upset participant’ is optional. Use it only if one of your participants appears upset during the debriefing.
6	You may not be able to cover everything in the script. That’s ok. Just try your best to follow the script content.
DO’S: DURING THE DEBRIEFING SESSION, ATTEMPT TO:	
1	Involve everyone in discussion and demonstrate respect for learners.
2	Allow students to self-reflect.
3	Cover the scenario learning objectives.
4	Use non-verbal communication (e.g. Head nods, eye contact, facial expressions and posture, proximity and distance) to encourage discussion.
5	Allow silence to give the participants time to think about questions.
6	USE ONE OR TWO VIDEO CLIPS. Suggestion for videos clips are highlighted in black. Run the clips for no more than 20-30 seconds.
DON’TS: DURING THE DEBRIEFING SESSION, AVOID :	
1	Dominating the debriefing session, or allowing one or two people to dominate the session.
2	Exacerbating participant’s issues with realism by arguing with them about what is realistic.

AIRWAY PROCEDURES

1. ET Intubation: Apneic Oxygenation: Amer J EM: 2019
2. ET Intubation: Bougie v ET Tube (Adult): JAMA: 2018
3. ET Intubation: Cricoid Pressure: Ped Crit Care Med: 2018
4. RSI: BVM Ventilation During RSI (Adult): NEJM: 2019

ENDOTRACHEAL INTUBATION: APNEIC OXYGENATION

In pediatric patients undergoing endotracheal intubation in the emergency department, is apneic oxygenation (high flow oxygen through a standard nasal cannula without ventilation), when compared to intubation without apneic oxygenation, associated with a decrease in hypoxemia (SpO_2 < 90%) during the procedure?

Michael Mojica, MD
June 2019

Vukovic AA, Hanson HR, Murphy SL, Mercurio D, Sheedy CA, Arnold DH.

APNEIC OXYGENATION REDUCES HYPOXEMIA DURING ENDOTRACHEAL INTUBATION IN THE PEDIATRIC EMERGENCY DEPARTMENT

Am J Emerg Med. 2019 Jan;37(1):27-32.
PubMed ID: 29699900

STUDY DEFINITIONS	
POPULATION	Inclusion: < 22 years of age Presenting to the emergency department Requiring endotracheal intubation (ETI) with/without rapid sequence medications Exclusion: Active cardiopulmonary resuscitation Unclear if apneic oxygenation received (After Apneic oxygenation group only) Setting: Single US Children's Hospital Before Apneic oxygenation cohort (Retrospective): 1/2011-6/2011 After Apneic oxygenation cohort (Prospective): 8/2014-3/2017
EXPOSURE	Apneic oxygenation: 100% FiO_2: 2 years: 4 Liters/min, > 2 to 12 years: 6 Liters/min, > 12 years: 8 Liters/min Delivered by a standard nasal cannula with wall oxygen Started by respiratory therapist as the standard of care at time of the decision to perform endotracheal intubation
NO EXPOSURE	No apneic oxygenation
CO-EXPOSURES	At discretion of treating physicians: 1. Preoxygenation method: Non-rebreather mask or bag-valve mask ventilation 2. Endotracheal intubation method: Direct/Video laryngoscopy, blade size/type
OUTCOME	Primary Outcome: Hypoxemia: SpO_2 < 90% during endotracheal intubation (ETI) Before ETI: Prior to sedation/paralysis OR Prior to mouth opening if without RSI During ETI: Mouth opening until the laryngoscope blade removed from mouth After ETI: Laryngoscope blade removal until confirmation of ET placement Multiple logistic regression: Potential patient/procedure confounding variables: Age, lowest SpO2 prior to ETI, proceduralist level of training/specialty, method of ETI (direct vs video laryngoscopy), number of ETI attempts
DESIGN	Observational: Retrospective cohort (before), prospective cohort (after)

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	Yes and No (Table 1). Patients in the before and after cohorts were similar with regard to age, gender, underlying medical conditions, lowest SpO_2 after ETI and number of ETI attempts. Patients were also similar with regard to indication for the ETI with the exception of altered mental status which was more frequent in the after apneic oxygenation group. Pediatric residents more commonly preformed ETI than emergency medicine residents and video laryngoscopy was performed more frequently in the after apneic oxygenation group. A logistic regression analysis was performed to account for the differences in potential confounders. It would have been helpful to include a comparison of patients moved from the after AO group to the before AO group because apneic oxygenation was not performed. However, a sensitivity analysis was performed excluding these patients and the study results did not change.
Were the circumstances and methods for detecting the outcome similar?	Yes. The same data collection form was used for both cohorts. A dedicated recording nurse completed the form at the time of the procedure. The data was kept in a standardized quality improvement database.
Was follow-up sufficiently complete?	Yes. The primary outcome was evaluated at the time of the procedure in the Emergency Department.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

N=149, 42% < 1 year of age
Before AO cohort: n=59 (including 14 who did not receive AO in the after AO time period)
After AO cohort: n=90

PRIMARY OUTCOME: HYPOXIA DURING ENDOTRACHEAL INTUBATION

	Before Apneic Oxygenation	After Apneic Oxygenation
Lowest SpO_2 (Median (IQR))	93% (69, 99%)	100% (95, 100%)
Hypoxemia (%)	50%	25%
25^{th}% of Lowest SpO_2*	69%	95%
*The authors considered a difference of ≥ 13% to be clinically significant		

REGRESSION: HYPOXIA DURING ENDOTRACHEAL INTUBATION

Independent Predictors	Adjusted Odds Ratio (95% CI)
Use of Apneic Oxygenation	0.3 (0.1, 0.8)
Age (every 1-year increase)	0.8 (0.7, 1.0)
SpO_2 before ETI (every 1% increase)	0.9 (0.8, 1.0)
Each addition attempt at ETI	4.0 (2.2, 7.2)
Proceduralist level of Training	0.7 (0.4, 1.3)
Method of Intubation (Direct/Video)	0.6 (0.1, 2.7)

RED = Not statistically significant, GREEN = Statistically significant
Beta coefficients not presented to allow for direct comparison of each variables predictive effect
Sensitivity analysis excluding patients transferred from the After AO cohort to the Before AO cohort resulted in similar adjusted odds ratios (Table 2)

HOW PRECISE IS THE ESTIMATE OF THE RISK?

The confidence intervals for the adjusted odds ratios are presented above. Risk and mean differences for the unadjusted analyses were not presented and not calculable from the data presented.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Likely. This was a single center study at a children's hospital in the US. In the after AO cohort the study center averaged approximately 3 intubations a month which is higher than our volume. It is unclear which sedatives and paralytics were used for those undergoing rapid sequence intubation.
Was follow-up sufficiently long?	Yes. The Primary outcome was hypoxemia during endotracheal intubation occurring in the ED.
Is the exposure similar to what might occur in my patient?	Yes. Endotracheal intubation is a rare but potentially life preserving procedure in the emergency department
What is the magnitude of the risk?	In the regression analysis patients in the after AO cohort were approximately 1/3 as likely to experience hypoxia (Adjusted odds ratio: 0.3, 95% CI (0.1, 0.8)).
Are there any benefits that offset the risks associated with exposure?	Only a single efficacy and no safety outcomes were presented. 4 patients were transferred to the before AO cohort from the after AO cohort because a seal could not be obtained for bag-valve mask ventilation. It is unclear if this was related to the presence of the nasal cannula. Risk differences for the primary outcome were not presented or calculable from the data presented so that a number needed to treat could not be determined.

CLINICAL BOTTOM LINE

BACKGROUND: Preoxygenation prior to intubation provides on oxygen reservoir during intubation in order to avoid hypoxemia. This is particularly important in children who have higher oxygen consumption than adults and become hypoxemic more quickly with rapid sequence intubation. Preoxygenation can be delivered with a non-rebreather face mask with or without bag-valve mask ventilation. Apneic oxygenation is the process of providing a high flow rate of oxygen through a standard nasal cannula prior to intubation without bag-valve mask ventilation. This should be distinguished from high flow, heated and humidified oxygen delivered by a proprietary devise. It is thought that the high flow rate results in nitrogen washout (replacing nitrogen with oxygen) which provides an oxygen reservoir as well as provides some degree of positive end expiratory pressure keeping airways open. Apneic oxygenation with a standard nasal cannula has the advantage of using readily available airway equipment, does not require removal prior to intubation (non-rebreather mask, noninvasive ventilation machines) and avoids the complications that can be associated with bag-valve-mask ventilation (abdominal distension resulting in vomiting and aspiration as well as limiting tidal volume due to increased intra-abdominal pressure due to gastric distension). Apneic oxygenation was been shown to be beneficial in adults but pediatric data is limited.

CLINICAL QUESTION: In pediatric patients undergoing endotracheal intubation in the emergency department, is apneic oxygenation (high flow oxygen through a standard nasal cannula without ventilation), when compared to intubation without apneic oxygenation, associated with a decrease in hypoxemia (SpO_2 < 90%) during the procedure?

DESIGN/RISK OF BIAS: This was a single-center observational study utilizing a retrospective “Before” apneic oxygenation (AO) cohort and prospective “After” AO cohort with a three-year interval between cohorts. The standard of care in the after AO cohort was apneic oxygenation defined as the delivery of 100% FiO_2 by a standard nasal cannula with wall oxygen and started by the respiratory therapist at the time that the decision to perform endotracheal intubation was made. The oxygen flow rate was determined by age. The preoxygenation method (non-rebreather mask or bag-valve mask ventilation) and endotracheal intubation method (direct or video laryngoscopy and the laryngoscope blade size and type) was at discretion of treating physicians. The primary outcome was the occurrence of hypoxemia (SpO_2 < 90%) during endotracheal intubation (ETI). During ETI was defined as the interval from mouth opening until the laryngoscope blade was removed from mouth.

Patients in the before and after cohorts were similar with regard to age, gender, underlying medical conditions, lowest SpO_2 after ETI and number of ETI attempts. Patients were also similar with regard to indication for the ETI with the exception that altered mental status which was more frequent in the after apneic oxygenation group. Pediatric residents more commonly performed ETI than emergency medicine residents and video laryngoscopy was performed more frequently in the after apneic oxygenation group. Multiple logistic regression was performed to account for the effect of patient and procedure specific confounding variables on the study outcome (Table 2).

13% (14/107) of the patients in the after apneic oxygenation era did not receive apneic oxygenation despite AO being defined as the standard or care. These patients were included in the before AO cohort. It would have been helpful to include a column in Table 1 comparing these patients to those who did receive AO in the after cohort and those in the before AO period. A sensitivity analysis excluding these patients did not reveal a difference in the study outcomes (Table 2). 4 of these patients did not receive

AO because a seal could not be obtained for bag-valve mask (BVM) ventilation. It is unclear if this was related to the presence of the nasal cannula. The proportion of patients successfully undergoing BVM ventilation with the cannula in place was not presented.

As with any before and after intervention design, there is a concern that something other than the intervention of interest changed between the study intervals. Pediatric resident intubation and video laryngoscopy were more common in the after AO cohort those there were not found to be independent predictors of hypoxia in the regression analysis.

PRIMARY RESULTS: 149 patients were included in the primary analysis of which 42% were less than 1 year of age. There were 59 patients on the Before AO cohort (including 14 who did not receive AO in the after AO time period) and 90 patients in the After AO cohort. Hypoxemia during endotracheal intubation was less common in the After AO cohort in both the univariable (unadjusted) analysis and the regression (adjusted) analysis (see tables below). The difference in the proportion with hypoxia was greater than the 13% difference indicated by the authors as clinically significant. Age, SpO_2 before endotracheal intubation and additional attempts at endotracheal intubation were also independent predictors of hypoxia during ETI.

PRIMARY OUTCOME: HYPOXIA DURING ENDOTRACHEAL INTUBATION		
	Before Apneic Oxygenation	After Apneic Oxygenation
Lowest SpO_2 (Median (IQR))	93% (69, 99%)	100% (95, 100%)
Hypoxemia (%)	50%	25%
25^{th}% of Lowest SpO_2*	69%	95%
*The authors considered a difference of ≥ 13% to be clinically significant		

REGRESSION: HYPOXIA DURING ENDOTRACHEAL INTUBATION	
Predictors	Adjusted Odds Ratio (95% CI)
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SpO_2 before ETI (every 1% increase)	0.9 (0.8, 1.0)
Each addition attempt at ETI	4.0 (2.2, 7.2)
Proceduralist level of Training	0.7 (0.4, 1.3)
Method of Intubation (Direct/Video)	0.6 (0.1, 2.7)
RED = Not statistically significant, GREEN = Statistically significant Beta coefficients not presented to allow for direct comparison of each variables predictive effect Sensitivity analysis excluding patients transferred from the After AO cohort to the Before AO cohort resulted in similar adjusted odds ratios	

APPLICABILITY: This was a single center study at a children's hospital in the US. It is likely that the study's results are applicable to those pediatric patients meeting the study's inclusion and exclusion criteria in that setting. However, in the after AO cohort the study center averaged approximately 3 intubations a month which is higher than our volume. It is also unclear which sedatives and paralytics were used for those undergoing rapid sequence intubation.

AUTHOR'S CONCLUSION: "In summary, in this observational analysis, utilizing apneic oxygenation was associated with reduced odds of hypoxemia during endotracheal intubation. Further, although a subset of patients in the apneic oxygenation group did experience hypoxemia, a larger proportion of patients not receiving the intervention experienced marked hypoxemia, with one quarter of patients having SpO_2 69% during endotracheal intubation. Providers should recognize the potential importance of this easily-applied intervention at reducing the incidence of hypoxemia during endotracheal intubation. Future studies should aim at optimizing endotracheal intubation attempts and reducing hypoxemia using randomized, controlled methodologies, as well as identifying other potentially modifiable interventions associated with this outcome."

POTENTIAL IMPACT: Apneic oxygenation is simple to perform and readily available in the Emergency Department. Its use in this study was associated with a statistical and clinical improvement in the proportion of patients with hypoxia during ETI. Since there are few if any adverse effects associated with its use it would seem prudent to recommend its routine use in the pediatric population. The potential for the nasal cannula to prevent an adequate seal during bag-valve mask ventilation merits further study. It is important to acknowledge that approximately one quarter of the patients in the after apneic oxygenation cohort experienced hypoxia leaving room for improvement and further evaluation of the other variables in the regression analysis that were found to be independent predictors of hypoxia during ETI. This question would benefit from a larger or multicenter clinical trial in the pediatric population.

ENDOTRACHEAL INTUBATION: BOUGIE VS ET TUBE & STYLET (ADULTS)

In adult patients, with at least one difficult airway characteristic, who are undergoing orotracheal intubation in the Emergency Department with a Macintosh laryngoscope blade, is use of a bougie with an endotracheal tube when compared to an endotracheal tube with a stylet, associated with greater first pass intubation success?

Michael Mojica, MD
July 2018

Driver BE, Prekker ME, Klein LR, Reardon RF, Miner JR, Fagerstrom ET, Cleghorn MR, McGill JW, Cole JB.

EFFECT OF USE OF A BOUGIE VS ENDOTRACHEAL TUBE AND STYLET ON FIRST-ATTEMPT INTUBATION SUCCESS AMONG PATIENTS WITH DIFFICULT AIRWAYS UNDERGOING EMERGENCY INTUBATION: A RANDOMIZED CLINICAL TRIAL
(BEAM TRIAL: BOUGIE USE IN EMERGENCY AIRWAY MANAGEMENT)

JAMA. 2018 Jun 5;319(21):2179-2189.
PubMed ID: 29800096

STUDY DEFINITIONS	
POPULATION	Inclusion: ≥ 18 years of age, underwent endotracheal intubation in the ED with a plan to use a Macintosh blade 1. Difficult airway characteristics* = 0 2. Difficult airway characteristics* ≥ 1 a. Body fluid obscuring laryngeal view b. Airway obstruction and/or edema c. Obesity d. Short neck and/or small mandible e. Large tongue f. Facial trauma g. C-spine immobilization *Subject assessment after intubation, explicit definitions not provided Exclusion: Prisoners, pregnant, known distortion of the airway or glottic structures (e.g. angioedema, epiglottitis, laryngeal mass or malignancy) Setting: Single academic level 1 trauma center, 9/2017-8/2017
INTERVENTION	Orotracheal intubation with a bougie (70 cm long, 15 French (5mm), semi-rigid, straight, single use, with a bent tip) MD discretion whether and how to bend the bougie 1. Operator passed the bougie into the trachea to the desired depth 2. Assistant loaded the ET tube over the bougie 3. Operator advanced ET tube into the trachea with laryngoscope in the mouth If resistance to ET tube passage, the ET tube retracted 2 cm, rotated 90^{o} counter-clockwise and re-advanced
CONTROL	Orotracheal intubation with endotracheal tube and stylet (straight to cuff shape with a distal bend angle of 25-35^{o}) If difficult passage, could withdraw, rotate, re-shape tube as needed Stylet in place until tube passed into trachea
CO-INTERVENTION	Intubation by EM faculty or resident (≥ PGY3) Residents trained with didactic, hands-on and simulation. Intubation experience in prior rotations At MD discretion • Positioning, pre-oxygenation, neuromuscular blockade, cricoid pressure • Choice of MAC laryngoscope: Direct or video (C-MAC, Glidescope), non-video If trachea not intubated with initial device, choice of subsequent equipment for the next attempt at MD discretion
OUTCOMES	Primary Outcome: First pass success defined as successful ET tube placement with the first device passed during the first laryngoscope insertion. Tube position confirmed with waveform capnography All intubations were video recorded until 1-minute following end of 1st attempt Secondary Outcomes: 1. Hypoxemia: O_2 saturation < 90% or ↓ of > 10% if initial saturation < 90% 2. First pass duration: Time from laryngoscope insertion to removal from mouth 3. Esophageal intubation
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Randomization was computerized using permuted blocks and stratified by 1. obesity and 2. cervical spine immobilization (either 1 or 2, neither 1 nor 2).
Was randomization concealed?	Yes. Intervention assignments were placed in sequentially numbered opaque envelopes. A research associate opened envelopes prior to laryngoscopy.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Treatment groups were similar with regard to demographic characteristics, indications for intubation and difficult airway characteristics (Table 1). Treatment groups were also similar with regard to intubation process measures (Table 2).
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Do to the nature of the interventions, physicians and research assistants could not be blinder.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. The trial intervention duration was short. Video of the procedure concluded 1 minute after the first intubation attempt.
Were patients analyzed in the groups to which they were randomized?	Yes. An intention to treat analysis was performed. In the all patients group 372/381 (97.5%) received the bougie as randomized and 345/376 (91.8%) received the ET tube with stylet as randomized. In the difficult airway group 191/198 (95.5%) received the bougie as randomized and 161/182 (88.5%) received the ET tube with stylet as randomized.
Was the trial stopped early?	No. Estimated 374 patients with at least 1 difficult airway characteristic required to demonstrate a 9% (95% vs 86%) difference in first pass intubation success (80% power, alpha error 0.05). 380 patients were included in the primary intention to treat analysis.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

n = 757 (all patients), bougie = 381, ET with stylet = 376
n = 380 (patients with difficult airway characteristics), bougie = 198, ET with stylet = 182
n = 51 emergency physicians, median intubations = 8, IQR 1-26, range 1-61

FIRST PASS INTUBATION SUCCESS

	Bougie**	ET Tube + Stylet	Risk Difference* (95%CI)
Difficult Airway ≥ 1	96% (191/198)	82% (150/182)	14% (8, 20%)
Difficult Airway = 0	99% (182/183)	92% (178/194)	8% (4, 12%)
All patients	98% (373/381)	87% (328/366)	11% (7, 14%)
C-spine Immobilized	100% (49/49)	78% (28/36)	22% (9, 66%)
Obesity	96% (55/57)	75% (51/68)	21% (10, 33%)
Cormack-Lehane 2-4	97% (101/104)	60% (54/90)	37% (26, 48%)
Blood/Vomit in Airway	95% (79/83)	82% (55/67)	13% (3, 23%)

*The authors considered a 9% difference to be clinically significant in their sample size analysis
**7% of bougie attempts required retraction and rotation of the ET tube
GREEN = Statistically significant difference, RED = No statistically significant difference

N = 56 (7%) first pass failure: Bougie (8), ET + Stylet (34)
2nd attempt success: Bougie (49), Intubating LMA (1), cricothyrotomy (1)

Attempt Duration (Figure 2)
All patients: Bougie = ET + Stylet
Difficult airway patients: Bougie < ET + Stylet

Complications (Table 5):
Any complication: Bougie 17%, ET + Stylet 17%
Hypoxemia: Bougie 13%, ET + Stylet 14%

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The confidence intervals for the risk difference presented above are moderate in width

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	These were adult patient presenting with a primarily medical indication for intubation. Unclear if the study's results could be generalized to pediatric patients. The study's first pass success with an ET tube and stylet is similar to what is reported in the literature.
Were all patient important outcomes considered?	Yes. All relevant intubation efficacy and adverse events were assessed
Are the likely treatment benefits worth the potential harm and costs?	NNT = 1/0.14 = 7. For every 7 patients with at least 1 difficulty airway characteristic who intubated with a bougie there would be 1 additional first pass success when compared to intubation with an ET tube and stylet. There were no differences in attempt duration or complications such as hypoxemia.

CLINICAL BOTTOM LINE

BACKGROUND: It is estimated that more than half of emergency department intubations can be classified as difficult. First pass success is approximately 85% and 12% of intubations are associated with adverse events. The bougie (aka tracheal tube introducer) is a long, semi-rigid device that is typically used when direct laryngoscopy fails or when there is a poor view of the vocal cords.

Use of the bougie is a 3-step process:
1. The bougie is passed into the trachea,
2. The endotracheal tube is advanced over the bougie into the trachea and
3. The bougie is removed from the trachea (VIDEO LINK: BOUGIE).

Potential benefits of the bougie include:
1. Airway visualization is less obscured than with an ET tube due to the bougie's smaller diameter
2. Allows passage of the tube with poor visualization of the airway due to upward bent tip
3. Tactile feedback: Positioning in trachea ("clicks") and insertion depth (resistance at carina)

CLINICAL QUESTION: In adult patients, with at least one difficult airway characteristic, who are undergoing orotracheal intubation in the Emergency Department with a MacIntosh laryngoscope blade, is use of a bougie with an endotracheal tube when compared to an endotracheal tube with a stylet, associated with greater first pass intubation success?

DESIGN/VALIDITY: This was a well-designed, randomized clinical trait conducted at a single academic center that is a level one trauma center. The primary population were adults with at least one characteristic suggestive of a difficult airway. The definition of difficult airway characteristics was not standardized and the assessment occurred after the intubation attempt. Patients were randomized to orotracheal intubation with a bougie or with an endotracheal tube with a stylet. Many aspects of the intubation were at the physician's discretion though these intubation process measures were similar in the two study groups. Physicians were attendings and at least PGY3 emergency medicine residents who were extensively trained in intubation techniques. It would have been helpful to stratify the results based on the level of training of the physician performing the intubation though an analysis based on clustering by physician did not significantly change the study results. The primary outcome was first pass success defined as successful ET tube placement with the first device passed during the first laryngoscope insertion.

PRIMARY RESULTS: The study included 757 patients. Of these 380 (50%) had at least one difficult airway characteristic. There was a statistically significant higher rate of first pass intubation success for the bougie group for: all patients, those with and without at least one difficult airway characteristics and for many of the individual difficult airway characteristics (See table below). The number needed to treat is 7 (NNT = 1/ARD = 1/0.14 = 7). For every 7 patients with at least 1 difficulty airway characteristic who are intubated with a bougie there would be 1 additional first pass success when compared to intubation with an ET tube and stylet. There was no difference in measured complications. A regression analysis was not conducted to account for the many potential confounding variables.

FIRST PASS INTUBATION SUCCESS			
	Bougie**	ET Tube + Stylet	Risk Difference* (95%CI)
Difficult Airway ≥ 1	96% (191/198)	82% (150/182)	14% (8, 20%)
Difficult Airway = 0	99% (182/183)	92% (178/194)	8% (4, 12%)
All patients (DF≥ 0)	98% (373/381)	87% (328/366)	11% (7, 14%)
C-spine Immobilized	100% (49/49)	78% (28/36)	22% (9, 66%)
Obesity	96% (55/57)	75% (51/68)	21% (10, 33%)
Cormack-Lehane 2-4	97% (101/104)	60% (54/90)	37% (26, 48%)
Blood/Vomit in Airway	95% (79/83)	82% (55/67)	13% (3, 23%)
*The authors considered a 9% difference to be clinically significant in their sample size analysis **7% of bougie attempts required retraction and rotation of the ET tube GREEN = Statistically significant difference, RED = No statistically significant difference			

APPLICABILITY: This is a single center study. It would have been helpful to know the rate of bougie use prior to study. The first pass success rate for a patient with a difficult airway with an ET tube and stylet is similar to what is generally presented in the literature.

These were adult patients presenting with a primarily medical indication for intubation. It is unclear if the study's results could be generalized to younger pediatric patients.

AUTHOR'S CONCLUSION: "In this emergency department, use of a bougie compared with an endotracheal tube plus stylet resulted in significantly higher first-attempt intubation success among patients undergoing emergency endotracheal intubation. However, these findings should be considered provisional until the generalizability is assessed in other institutions and settings."

POTENTIAL IMPACT: This was a well-designed, clinical trial that demonstrated a statistically significant improvement in first pass intubation success with a bougie for all patients, as well as those with and without difficult airway characteristics. There were no adverse events associated with bougie use when compared to use of an endotracheal tube and stylet. The findings suggest that bougie could be used as a primary device and not considered a secondary option for when direct laryngoscopy and endotracheal tube placement fails. This was a single center study and the results require further validation in other settings before a change in clinical practice occurs. However, it may be prudent to ensure that a bougie is readily available for all intubation attempts.

ENDOTRACHEAL INTUBATION: CRICOID PRESSURE

In patients less than 18 years of age, undergoing intubation in the pediatric intensive care unit using direct laryngoscopy, is cricoid pressure during induction and mask ventilation associated with a lower regurgitation rate?

Nisha Narayanan, MD., Alvira Shah, MD.
June 2018

Kojima T, Harwayne-Gidansky I, Shenoi, AN, Owen EB, Napolitano N, Rehder KJ; Adu-Darko MA, Nett ST, Spear D, Meyer K, Guiliano JS, Tarquinio KM, Sanders RC, Lee JH, Simon DW, Vanderford PA, Lee AY, Brown CA, Skippen PW, Breuer RK, Toedt-Pingel I, Parsons SJ, Gradidge EA, Glater LB, Culver K, Nadkarni VM, Nishisaki A.

CRICOID PRESSURE DURING INDUCTION FOR ENDOTRACHEAL INTUBATION IN CRITICALLY ILL CHILDREN: A REPORT FROM NATIONAL EMERGENCY AIRWAY REGISTRY FOR CHILDREN.

Pediatric Critical Care Medicine. 2018 June. 19(6):528–537.
PubMed ID: 29863636

STUDY DEFINITIONS	
POPULATION	Inclusion: Pediatric ICU patients < 18 years of age undergoing endotracheal intubation using direct laryngoscopy. Exclusion: Endotracheal tube replacement Tracheostomy Laryngeal mask placement Intubation facilitated by video laryngoscopy or fiberoptic bronchoscopy Setting: 35 PICUs within general and children's hospitals (United States (29), Canada (3), Japan (1), Singapore (1), New Zealand (1). 7/2010-12/2015 National Emergency Airway Registry for Children (NEAR4 Kids) (A multicenter Pediatric ICU quality improvement collaboration)
EXPOSURE	Use of cricoid pressure during induction and mask ventilation prior to laryngoscopy Cricoid Pressure: Defined as providing external pressure on the anterior aspect of the patient's cricoid cartilage during induction and mask ventilation prior to laryngoscopy External Laryngeal Manipulation: Defined as manipulating the thyroid cartilage to improve glottis view performed during laryngoscopy and insertion of the ET tube
NO EXPOSURE	No use of cricoid pressure during induction and mask ventilation prior to laryngoscopy
OUTCOME	Primary Outcome: Regurgitation Defined as clinical evidence of gastric contents reflux from initiating bag-mask ventilation until completion of ET tube placement in the trachea. Documented when there was evidence of regurgitation in the oral cavity during induction or mask ventilation or visible gastric content in the pharynx during laryngoscopy Secondary Outcome: Clinical aspiration Defined as clinical evidence of gastric contents in the trachea (e.g. gastric contents suctioned from the trachea after endotracheal tube placement, decision and timing for endotracheal suction after intubation was made at provider discretion)
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	No. Tables 1 and 2 show that cricoid pressure and non-cricoid pressure groups were NOT similar. Age, indication for endotracheal intubation, impaired airway reflexes, unstable hemodynamics, procedure, any difficulty airway feature, difficult mask ventilation, rapid sequence, and opioid usage were not similar. Adjustments were made using two statistical methods: multiple logistic regression and propensity score matching.
Were the circumstances and methods for detecting the outcome similar?	Yes. This was a retrospective chart review. Data was extracted from the National Emergency Airway Registry for Children (NEAR-4KIDS), a large international PICU QI collaborative. Operational definitions were implemented with high compliance at participating sites including specific definitions for cricoid pressure which were differentiated from external laryngeal manipulation during laryngoscopy. The data was prospectively collected by clinicians at the time of each endotracheal intubation following by a standardized data verification process by each site project. The data was extracted from the database using a standardized data collection form.
Was follow-up sufficiently complete?	Yes. Given that the occurrence of regurgitation was defined as clinical evidence of gastric contents reflux from initiating bag-mask ventilation until completion of ET tube placement in the trachea, follow-up would be considered sufficient for this study as long as the patient was monitored until completion of ET tube placement.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

Primary Outcome: Occurrence of Regurgitation
Prevalence:

	Regurgitation		
	YES	NO	
Cricoid Pressure	35	1,784	1,819
No Cricoid Pressure	71	5,935	6,006
	106	7,719	7,825

Cricoid Pressure: 1,819/7,825 = 23.2%
Regurgitation: 106/7,825= 1.4%
Clinical aspiration with regurgitation: 51/7,825= 0.7%

Regurgitation
Cricoid Pressure: 35/1,819 = 1.9%
No Cricoid Pressure: 71/6,006 = 1.2%
Risk Difference: 0.7%, 95% CI (0.1, 1.5%)
Relative Risk: 0.19/0.12 = 1.6 (1.1, 2.4)
Unadjusted odds ratio: (35/71)/(1,784/5,935) = 0.49/0.30 = 1.64, 95% CI (0.99, 2.47)

Regression Analysis:
Patient and practice factors included age, indication for endotracheal intubation, impaired airway reflexes, unstable hemodynamics, procedure, any difficulty airway feature, difficulty mask ventilation, rapid sequence, and opioid usage.

Adjusted odds ratio: 1.57, 95% CI (0.99, 2.47)

Sensitivity Analysis: Propensity score matching generated 1,194 matched pairs in the cricoid pressure and no cricoid pressure groups (31% (2,388/7,825) of the study population).
Baseline differences in patient and care actors were well-balanced after matching (Table 4).
Patient's age (> 8 years) and hemodynamic instability were risk factors for regurgitation.
These risk factors remained the same when the sub-cohort of children with cricoid pressure was evaluated (Supplemental Table 1).

Primary Outcome: Occurrence of Regurgitation in the Propensity Matched Cohort

	Regurgitation		
	YES	NO	
Cricoid Pressure	25	1,169	1,194
No Cricoid Pressure	14	1,180	1,194
	39	2,349	2,388

Prevalence:
Cricoid Pressure: Given that this is a propensity-matched cohort, there are equal numbers of patients with and without cricoid pressure
Regurgitation: 39/ 2,388 = 1.6%

Regurgitation:
Cricoid Pressure: 25/1,194 = 2.1%
No Cricoid Pressure: 14/1,194 = 1.2%
Risk Difference: 0.9%, 95% CI (-0.1, 2.0%)
Relative Risk: 2.1/1.2 = 1.8, 95% CI (0.9, 3.4)
Adjusted odds ratio: 1.01, 95% CI (1.00, 1.02)

HOW PRECISE IS THE ESTIMATE OF THE RISK?

The confidence intervals for the odds ratios provided above are relatively narrow given the study's large sample size.

For the primary outcome after multivariable regression analysis, the confidence interval for the adjusted odds ratio does includes 1. This indicates that there is not a statistically significant difference between the use of cricoid pressure and regurgitation (Adjusted odds ratio: 1.57, 95% CI (0.99-2.47)

For the primary outcome after sensitivity analysis, the confidence interval for the adjusted odds ratio does include 1. This indicates that there is a statistically significant difference between cricoid pressure and regurgitation after adjusting for patient and process of care confounders.
Adjusted odds ratio: 1.01, 95% CI (1.00, 1.02)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Unclear. The study patients were all critically ill children who received endotracheal intubations in the PICUs by non-anesthesiologists. The study patients were likely similar to the patients seen at Bellevue and Tisch hospital who would require intubation, but are not similar to general pediatric ED patients because this study was performed on patients in the ICU with a higher severity of illness. The patients in the study were more likely to be NPO prior to intubation, unlike patients in the ED requiring emergent endotracheal intubation which would decrease their risk of regurgitation.
Was follow-up sufficiently long?	Yes. Given that the occurrence of regurgitation was defined as clinical evidence of gastric contents reflux from initiating bag-mask ventilation until completion of ET tube placement in the trachea, follow-up would be considered sufficient for this study as long as the patient was monitored until completion of ET tube placement.
Is the exposure similar to what might occur in my patient?	Unclear. Providing cricoid pressure during intubation is commonly applied during induction and mask ventilation before high-risk endotracheal intubation in critically ill children to prevent regurgitation and aspiration in PICUs. However, it is a provider-specific decision. At Bellevue and Tisch EDs, this is not a standard protocol that is followed.
What is the magnitude of the risk?	Those patients who had cricoid pressure applied during endotracheal intubation were not more likely to have regurgitation. The risk differences in the regression and propensity matching analyses for the cricoid pressure and no cricoid pressure groups were less than 1% with a high risk (though not significantly so) in the cricoid pressure group.
Are there any benefits that offset the risks associated with exposure?	The exposure, the presence of cricoid pressure during intubation, was not associated with an increased risk for the primary outcome, regurgitation. However, nobody monitored each cricoid pressure method provided by critical care providers or the actual effectiveness of cricoid pressure in occluding the esophagus. Thus, it is possible that improperly applied cricoid pressure might have increased risk of regurgitation. Cricoid pressure may also decrease lower esophageal sphincter tone which may increase the risk of reflux of gastric contents, may induce a gag reflex in awake adult patients, and may cause laryngeal distortion, possibly hindering intubation. Thus, these theoretical negative aspects of cricoid pressure might have resulted in a higher occurrence of regurgitation with cricoid pressure use.

CLINICAL BOTTOM LINE

BACKGROUND: The use of cricoid pressure during mask ventilation prior to high-risk endotracheal intubation was advocated in the past to prevent gastric insufflation, regurgitation, and aspiration during induction of anesthesia. However, there is limited evidence to support cricoid pressure's effectiveness to prevent regurgitation in critically ill children. The 2010 American Heart Association PALS guidelines state that: "There is insufficient evidence to recommend routine cricoid pressure application to prevent aspiration during endotracheal intubation in children. Do not continue cricoid pressure if it interferes with ventilation or the speed or ease of intubation" (AHA, Circulation 2010, PubMed ID: 20956230). Cricoid pressure with an intent to occlude the esophagus to prevent regurgitation should be distinguished laryngeal manipulation with the intent of improve airway visualization during laryngoscopy. Laryngeal manipulation may be more helpful in children due to a more anterior airway relative to the anterior mandible.

CLINICAL QUESTION: In patients less than 18 years of age undergoing intubation in the pediatric intensive care unit using direct laryngoscopy, is cricoid pressure during induction and mask ventilation associated with a lower regurgitation rate?

DESIGN/RISK OF BIAS: This was a well-designed retrospective cohort study utilizing a multicenter pediatric airway quality improvement registry with a sample size of 7,825 endotracheal intubations. The exposure of interest was the use of cricoid pressure defined as providing external pressure on the anterior aspect of the patient's cricoid cartilage during induction and mask ventilation prior to laryngoscopy. This was distinguished from external laryngeal manipulation which was defined as manipulating the thyroid cartilage to improve glottis view performed during laryngoscopy and insertion of the ET tube. The primary outcome was regurgitation defined as clinical evidence of gastric contents reflux from initiating bag-mask ventilation until completion of ET tube placement in the trachea. This was documented when there was evidence of regurgitation in the oral cavity during induction or mask ventilation or visible gastric content in the pharynx during laryngoscopy. Both multiple logistic regression and propensity matching were used to account for confounding variables.

The authors identified potential study limitations including

1. The NEAR4KIDS registry relies on self-reporting. There may be inaccuracies and reporting biases despite the use of well-established operational definitions to minimize these biases. It is also possible that providers reported the use of cricoid pressure more often when clinical regurgitation was observed in order to justify their endotracheal intubation practice, which could have biased the result away from the null hypothesis.
2. The timing of the regurgitation during endotracheal intubation was not documented.
3. It is unknown whether cricoid pressure was performed correctly with respect to anatomical location, direction, and force. Therefore, it is possible that improperly applied cricoid pressure might have increased the risk of regurgitation.
4. No information presented regarding fasting interval and gastric distension from bag-mask ventilation
5. The study was not able to account for some potential confounders that were previously reported risk factors for aspiration, including prior/current surgical or medical problems.

PRIMARY RESULTS: 23.2% (1,819/7,825) of all patients received cricoid pressure during intubation. 1.4% (106/7,825) of all patients had an occurrence of regurgitation and 0.7% (51/7,825) had an occurrence of clinical aspiration with regurgitation. Regurgitation was reported in 1.9% (35/1,819) of patients with cricoid pressure and 1.2% (71/6,006) of patients without cricoid pressure (unadjusted risk difference: 0.7%, 95% CI (0.1, 1.5%), unadjusted odds ratio: 1.64; 95% CI (1.09, 2.47).

On multivariable logistic regression analysis, cricoid pressure was not associated with the occurrence of regurgitation after adjusting for patient, practice, and known regurgitation risk factors (adjusted odds ratio, 1.57; 95% CI (0.99, 2.47). Propensity score matching generated 1,194 matched pairs in the cricoid pressure and no cricoid pressure groups (31% (2,388/7,825) of the study population). Cricoid pressure not associated with a slightly higher regurgitation rate (adjusted odds ratio, 1.01, 95% CI (1.00, 1.02).

APPLICABILITY: The study data included patients form 35 different PICUs within general and children's hospitals in the United States, Canada, Japan, Singapore and New Zealand. The study's results can likely be generalized to critically ill patients requiring endotracheal intubation by non-anesthesiologist in the PICU meeting the study's inclusion and exclusion criteria. The study results applicability in the emergency department is unclear.

AUTHOR'S CONCLUSION: "In conclusion, cricoid pressure is commonly applied during induction and mask ventilation before high-risk endotracheal intubation in critically ill children to prevent regurgitation and aspiration in PICUs. Cricoid pressure use in the current PICU practice was not associated with a lower occurrence of regurgitation in PICU practice after adjusting for patient risk factors. Future prospective investigation is needed to evaluate whether the use of cricoid pressure with specific indication and proper procedural approach would be effective in decreasing the occurrence of regurgitation and aspiration."

POTENTIAL IMPACT: Cricoid pressure is often used to prevent regurgitation during induction and mask ventilation prior to high-risk endotracheal intubation in children. However, there is confusion regarding whether this actually confers an advantage to patients and concern that it may actually cause harm. This study demonstrated that cricoid pressure during induction and mask ventilation before endotracheal intubation is not associated with a lower regurgitation rate after adjusting for previously reported confounders. This was a study with a large and diverse patient population that can be applied to most pediatric ICU settings but not necessarily to pediatric ED settings. If applied, this study could lead to decreased confusion regarding the utility of cricoid pressure during the endotracheal intubation of critically ill children and support the 2010 American Heart Association recommendations.

RAPID SEQUENCE INTUBATION: BAG-VALVE-MASK VENTILATION (ADULT)

In critically ill adults undergoing rapid sequence intubation does positive-pressure ventilation with a bag-valve-mask device when compared no ventilation in the interval between induction (administration of a sedative and paralytic agent) and laryngoscopy reduce hypoxemia without an increase in aspiration?

Nisha Narayanan M.D., Kavita Patel M.D.
September 2019

Casey JD, Janz DR, Russell DW, Vonderhaar DJ, Joffe AM, Dischert KM, Brown RM, Zouk AN, Gulati S, Heideman BE, Lester MG, Toporek AH, Bentov I, Self WH, Rice TW, Semler MW.

BAG-MASK VENTILATION DURING TRACHEAL INTUBATION OF CRITICALLY ILL ADULTS.

N Engl J Med. 2019 Feb;380(9):811-21.
PubMed ID: 30779528

STUDY DEFINITIONS	
POPULATION	Inclusion: Adult (≥18 years) ICU patients Undergoing induction (sedation ± paralytic) and endotracheal intubation (ETI) Exclusion: Pregnant Incarcerated Immediate need for tracheal intubation precluding randomization Ventilation between induction and laryngoscopy was: a. Required (e.g. as treatment for hypoxemia or severe acidemia) OR b. Contraindicated (e.g. ↑ aspiration risk, emesis, hematemesis, hemoptysis) Setting: 7 Academic ICUs (US), 3/2017-5/2018
INTERVENTION	Bag-Valve-Mask (BVM) ventilation between induction and laryngoscopy O_2 at ≥ 15 liters/minute Peep valve at 5-10 cm H_2O Oropharyngeal airway 2 handed mask seal Head tilt-chin lift Ventilated at 10 breaths/minute with smallest volume required for chest rise
CONTROL	No Bag-Valve-Mask (No BVM) ventilation between induction and laryngoscopy Oxygen was permitted at clinician discretion BVM ventilation was permitted at clinician discretion if: a. Failed ETI attempt b. Oxygen saturation < 90%
CO-INTERVENTIONS	ETI performed primarily by ICU fellows and anesthesia residents with more the 50 prior ETIs Non-invasive ventilation not allowed during study time interval Pre-induction management at treating clinician discretion including pre-oxygenation, non-invasive ventilation
OUTCOME	Primary Outcome: Lowest oxygen saturation observed during the interval between induction and 2 minutes after tracheal intubation (measured by continuous pulse oximetry) Secondary Outcome: Severe hypoxemia (O_2 saturation < 80%) during the study time interval Tertiary Outcome: Gastric Aspiration • Operator-reported oropharyngeal or gastric aspiration during ETI • New opacity on chest x-ray in the 48 hours after tracheal intubation • Clinical manifestations of periprocedural or oropharyngeal gastric aspiration 6-24 hours after tracheal intubation (Worst value of: O_2 saturation, fraction of inspired oxygen required, positive end-expiratory pressure required)
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients underwent randomization in a 1:1 ratio to undergo either bag-valve-mask ventilation or no bag-valve-mask ventilation in permuted blocks of 2, 4, and 6, stratified by trial site.
Was randomization concealed?	Yes. Trial group assignments were placed in sequentially numbered opaque envelopes and remained concealed until after enrollment.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. The significant differences in baseline characteristics between the two trial groups were the proportion of patients with pneumonia (57% in BVM, 80% in no BVM) and gastrointestinal bleeding (31% in BVM, 18% in no BVM) (Table 1: Patient Characteristics). Patients in the BVM group (39.7%) were statistically more likely to receive BVM ventilation for pre-oxygenation than patients in the No BVM group (10.9%) (RR 3.65 (2.37, 5.6). Patients in the BVM group (11.6%) were statistically less likely to receive high-flow oxygen via nasal cannula for pre-oxygenation than patients in the No BVM group (20.3%) (RR 0.57, 0.36, 0.91). Patients in the BVM group (100%) were statistically more likely to receive supplemental oxygen in the interval between induction and laryngoscopy than patients in the No BVM group (77%). 21.8% of the patients in the No BVM group received BVM ventilation for any indication between induction and ETI (Table 3: Procedure Characteristics). A regression analysis included 11 potential confounding variables.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study was not blinded. Given the nature of the intervention, patients, clinicians, and research personnel were aware of the trial-group assignments after the randomization. The authors acknowledge that knowledge of the study group may have influenced decisions regarding pre-induction management such as the method of pre-oxygenation.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Data was available for 100% (401/401) of patients.
Were patients analyzed in the groups to which they were randomized?	Yes. 100% (401/401) of patients were included in the primary intention to treat analysis. A per protocol analysis was performed as well, which compared patients who had received bag-mask ventilation to prevent hypoxemia before the first attempt at laryngoscopy to those who had not received bag-valve-mask ventilation. A total of 99.5% (198/199) of patients in the bag-mask ventilation group received bag-mask ventilation. 97.5% (197/202) patients in the no-BVM group do not receive BVM ventilation.
Was the trial stopped early?	No. The trial was not stopped early.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N= 401 (BMV: 199, no BVM: 202)
Sedative use: 100%, Paralytic use: 97.5%
First ETI Attempt Success: BVM 83.9%, No BVM 80.2% (Table S11)
Median O_2 saturation at induction: BVM 99%, IQR (95,100), No BVM 99%, IQR (96, 100)

Time from Induction to Laryngoscopy (Table 2):
BVM: 98 seconds, IQR (65, 135 seconds)
No BVM: 72 seconds IQR (52, 120 seconds)
Mean Difference: 13.8 seconds, 95% CI (-1.1, 28.6 seconds)

Indications for Intubation (Table S4):
1. Hypoxemic respiratory failure: BVM 58.8%, No BVM 57.4%
2. Hypercarbic respiratory failure: BVM 19.6%, No BVM 27.2%
3. Air protection for ↓ level of consciousness: BVM 37.2%, No BVM 37.6%

OUTCOMES

	Bag-Valve-Mask Ventilation	No Bag-Valve-Mask Ventilation	Relative Risk[1] or Mean difference[2]
HYPOXIA (EFFICACY)			
1° Lowest O_2 Sat (Median (IQR))	96% (87, 99%)	93% (81, 99%)	3.9% (1.4, 6.5%)[2, 3]
2° O_2 Sat < 80%	10.9% (21/193)	22.8% (45/197)	0.48 (0.30, 0.77)[1]
ASPIRATION (SAFETY)			
Operator-reported aspiration	2.5% (5/199)	4.0% (8/202)	0.63 (0.21, 1.91)[1]
New opacity on Chest XRAY	16.4% (31/189)	14.8% (29/186)	1.11 (0.70, 1.77)[1]
Lowest O_2 Sat 6-24 hours (IQR)	94% (91, 97%)	94% (91, 97%)	-0.2% (-1.9, 1.4%)[2]
Highest FiO_2 6-24 hours (IQR)	50% (40, 70%)	50% (40, 70%)	-0.0% (-10. 0.0%)[2]
Highest PEEP 6-24 hours (IQR)	5 (5, 8)	5 (5, 8)	0.1, (-0.7, 0.5)[2]

GREEN = Statistically significant, RED = Not statistically significant
1. Relative Risk (95% CI)
2. Mean Difference (95% CI)
3. Regression analysis: Adjusted mean difference: 4.7%, 95% CI (2.8, 7.5%)
Authors considered a 5% difference to be clinically significant in their sample size determination
No difference in 1° outcome between intention-to-treat and per-protocol analysis (Table S13)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Due to the large sample size (n=401), the confidence intervals for the primary outcome (3.9%, 95% CI (1.4, 6.5%) and the secondary outcomes (0.48, 95% CI (0.30, 0.77) are narrow.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patients?	No. Study patients were critically ill adults (≥ 18 years) in the ICU. Children have a lower oxygen reserve than adult patients. In addition, ED patients are more likely to have a full stomach and therefore a higher risk of aspiration.
Were all patient important outcomes considered?	Yes. The study included multiple efficacy and safety outcomes. In addition, a number of subgroup analyses (Figure 2) exploratory outcomes (Table 3 and supplementary materials) were presented. These included patient relevant outcomes.
Are the likely treatment benefits worth the potential harm and costs?	Yes. The lowest oxygen saturation was 3.9% higher among patients assigned to receive bag-valve-mask ventilation than among those assigned to not receive bag-valve-mask ventilation from induction to laryngoscopy. The absolute percentage of patients who had severe hypoxemia was 12% lower in the bag-valve mask ventilation group. The corresponds to a number needed to treat of 9 (NNT = 1/ ARD = 1/0.12 = 9). This indicates that for every 9 critically ill adults undergoing tracheal intubation, providing bag-valve-mask ventilation between induction and laryngoscopy would prevent severe hypoxemia in 1 additional patient.

CLINICAL BOTTOM LINE

BACKGROUND: Hypoxemia is one of the most common complications during tracheal intubation and may lead to cardiac arrest and death. Rapid-sequence induction is the use of medications (sedative and paralytic) to facilitates intubation. There is debate whether providing positive-pressure ventilation with a bag-valve-mask device during the interval between administration of induction medications and laryngoscopy prevents hypoxemia without increasing the risk of gastric aspiration.

CLINICAL QUESTION: In critically ill adults undergoing rapid sequence intubation does positive-pressure ventilation with a bag-valve-mask device when compared no ventilation in the interval between induction (administration of a sedative and paralytic agent) and laryngoscopy reduce hypoxemia without an increase in aspiration?

DESIGN/VALIDITY: The was a multicenter, randomized trial of 401 adult patients requiring endotracheal in the ICU. It was well designed and included randomization to balance baseline confounders, concealment of group assignment until enrollment to prevent selection bias, the conduct of trial at multiple centers to increase generalizability, and the collection of trial end points by an independent observer to minimize observation bias. Rates of protocol noncompliance and missing data were low. However, the nature of the trial intervention did not allow blinding, and knowledge of group assignment may have contributed to differences in pre-oxygenation technique between groups.

The BVM group received positive pressure ventilation and oxygen during the interval between induction and laryngoscopy. The No BVM group did not receive positive pressure ventilation and could receive oxygen at the discretion of the clinical provider (77% received oxygen). The authors justify making the use of oxygen optional because “a previous trial in a similar setting showed no benefit for the use of supplemental oxygen without ventilation during the interval between induction and tracheal intubation”. It would have been helpful to include a subgroup analysis comparing the BVM group to the No BMV group who received oxygen and the No BVM group those who did not receive oxygen. A 2019 study of pediatric apneic oxygenation in the emergency department demonstrated that apneic oxygenation was associated with a statistical and clinical improvement in the proportion of patients with hypoxia during ETI. (Vukovic, Am J Emerg Med. 2019, PubMed ID: 29699900). There were a number of statistically significant differences in both the patient and intubation characteristics that were accounted for in the regression analysis.

The study outcomes include assessment of efficacy (oxygenation) and safety (aspiration). The primary efficacy outcome was the lowest oxygen saturation observed during the interval between induction and two minutes after tracheal intubation. This is a composite interval including: Induction to Laryngoscopy, Laryngoscopy to successful ETI and Successful ETI until 2 minutes after Successful ETI. Hypoxia occurring in the latter 2 intervals could be the results of ETI and not due to whether ventilation was performed in the interval between induction and laryngoscopy. It would have been helpful to have the analysis stratified for each of these three, time intervals.

PRIMARY RESULTS: The study demonstrated that the median lowest oxygen saturation between induction and two minutes after tracheal intubation was higher in the BVM group (96%, IQR (87, 99)) than in the No BVM group (93%, IQR (81-99) (Mean Difference 3.9% (1.4, 6.5%), adjusted mean difference, 4.7%, 95% CI (2.8, 7.5%)). While this difference is statistically significant, it does not meet the criteria of a 5% difference as clinically significant in the sample size determination. In addition, the clinical importance of the difference in the risk of hypoxia is unclear.

Fewer patients in the BVM group (10.9%) had severe hypoxemia than in the No BVM group (22.8%), RR 0.48, 95% CI (0.30, 0.77)). The absolute percentage of patients who had severe hypoxemia was 12% lower in the bag-valve mask ventilation group. The corresponds to a number needed to treat of 9 (NNT = 1/ARD = 1/0.12 = 9). For every 9 critically ill adults undergoing tracheal intubation, providing bag-valve-mask ventilation between induction and laryngoscopy would prevent severe hypoxemia in 1 additional patient.

Operator-reported aspiration occurred during 2.5% of intubations in BVM group and 4.0% in the no BVM group (Relative Risk; 0.63, 95% CI (0.21, 1.91). The incidence of new opacity on chest radiography in the 48 hours after tracheal intubation was 16.4% and 14.8% respectively (Relative Risk: 1.11, 95% CI (0.70, 1.77). The was no difference in the lowest oxygen saturation, highest FiO_2 or highest PEEP required in the 6-24 hours post intubation. However, the incidence of aspiration was low (Operator report aspiration (3.2%), new Chest XRAY opacity (15%)) and there may have been insufficient power to identify a statistically significant difference.

In prespecified subgroup analysis, the difference in the lower oxygen saturation between the bag-mask ventilation group and the no-ventilation group was greater for patients with lower oxygen saturation at induction. None of the other prespecified characteristics, including body-mass index, score on APACHE II, and operator experience, appeared to modify the effect of bag-mask ventilation on the lower oxygen saturation.

OUTCOMES			
	Bag-Valve-Mask Ventilation	No Bag-Valve-Mask Ventilation	Relative Risk[1] or Mean difference[2]
HYPOXIA (EFFICACY)			
1° Lowest O_2 Sat (Median (IQR))	96% (87, 99%)	93% (81, 99%)	3.9% (1.4, 6.5%)[2, 3]
2° O_2 Sat < 80%	10.9% (21/193)	22.8% (45/197)	0.48 (0.30, 0.77)[1]
ASPIRATION (SAFETY)			
Operator-reported aspiration	2.5% (5/199)	4.0% (8/202)	0.63 (0.21, 1.91)[1]
New opacity on Chest XRAY	16.4% (31/189)	14.8% (29/186)	1.11 (0.70, 1.77)[1]
Lowest O_2 Sat 6-24 hours (IQR)	94% (91, 97%)	94% (91, 97%)	-0.2% (-1.9, 1.4%)[2]
Highest FiO_2 6-24 hours (IQR)	50% (40, 70%)	50% (40, 70%)	-0.0% (-10. 0.0%)[2]
Highest PEEP 6-24 hours (IQR)	5 (5, 8)	5 (5, 8)	0.1, (-0.7, 0.5)[2]

GREEN = Statistically significant, RED = Not statistically significant
1. Relative Risk (95% CI)
2. Mean Difference (95% CI)
3. Regression analysis: Adjusted mean difference: 4.7%, 95% CI (2.8, 7.5%)
Authors considered a 5% difference to be clinically significant in their sample size determination
No difference in 1° outcome between intention-to-treat and per-protocol analysis (Table S13)

APPLICABILITY: Enrolling patients at multiple centers likely makes the results applicable to adult ICU patients requiring intubation who meet the studies inclusion and exclusion criteria. It is unclear whether this study can be applied to academic pediatric emergency department patients. Children have a lower oxygen reserve than adults. In addition, ED patients are more likely to have a full stomach and therefore have a higher risk of aspiration.

AUTHOR'S CONCLUSION: "In this multicenter, randomized trial involving critically ill adults undergoing tracheal intubation, patients receiving bag-mask ventilation during the interval between induction and laryngoscopy had higher oxygen saturations and lower rates of severe hypoxemia than those receiving no ventilation."

POTENTIAL IMPACT: The study has 2 primary risk of bias concerns. The first is that only 77% in the No BVM group received oxygen during the interval between induction and laryngoscopy (BVM group 100%). The second is that the primary efficacy outcome was the lowest oxygen saturation observed during the interval between induction and 2 minutes after tracheal intubation. This is a composite time interval that includes: Induction to Laryngoscopy, Laryngoscopy to successful ETI and successful ETI until 2 minutes after successful ETI. Hypoxia occurring in the latter 2 intervals could be the results of ETI and not due to whether ventilation was performed in the interval between induction and laryngoscopy. These 2 concerns could have been resolved with subgroup analyses.

The study demonstrated a higher risk of hypoxia in both the primary and secondary outcome in the No BVM group. In the primary outcome, the adjusted mean difference in oxygen saturation was 4.7%, 95% CI (2.8, 7.5%). The clinical relevance of this difference is unclear. The authors indicated a 5% difference to be clinically significant in their sample size determination. The use of BVM ventilation in the interval between induction and laryngoscopy was not associated with an increased risk of aspiration. However, the incidence of aspiration was low (Operator report aspiration (3.2%), new Chest XRAY opacity (15%)) and there may have been insufficient power to identify a statistically significant difference.

This was a study of critically ill adults in the ICU. Generalizable to the pediatric population with a lower oxygen reserve and the ED population who have a higher likelihood of a full stomach and therefore a higher risk of aspiration is unclear. The trial did not examine the use of noninvasive ventilation during the interval between induction and laryngoscopy.

CARDIOLOGY

1. ED Discharge Tachycardia: Annals of Emerg Med. 2017
2. Ondansetron: QT Prolongation: Pediatr Emerg Care 2016

CARDIOLOGY:
ED DISCHARGE TACHYCARDIA

In patients less than 19 years of age, is tachycardia at the time of discharge from the ED or urgent care center associated with increased risk of revisit within 72 hours or the receipt of clinically important interventions, or hospital admission on revisit?

Kelsey Fawcett, MD., Rebecca Burton, MD.
July 2017

Wilson PM, Florin TA, Huang G, Fenchel M, Mittiga MR.

IS TACHYCARDIA AT DISCHARGE FROM THE PEDIATRIC EMERGENCY DEPARTMENT A CAUSE FOR CONCERN? A NON-CONCURRENT COHORT STUDY

Ann Emerg Med. 2017 Sep;70(3):268-276.e2
PubMed ID: 28238501

STUDY DEFINITIONS	
POPULATION	Inclusion: < 19 years treated and discharged from the ED's or urgent care center Exclusion: Children without a documented pulse rate Setting: Medical Center with 2 freestanding Children's hospitals (1 urban, 1 suburban), and 4 urgent care centers (1 urban, 3 suburban), 1/2013-12/2013
EXPOSURE	Tachycardia (> 99th percentile for age) at the time of discharge
NO EXPOSURE	Normal heart rate for age at time at the time of discharge
OUTCOME	Primary Outcome: Unscheduled revisit to ED or urgent care within 72 hours Secondary Outcomes: 1. Receipt of clinically important interventions at time at revisit 2. Association of pain, fever, and medications with discharge tachycardia 3. Temporal relationship of the final documented pulse rate at discharge 4. Diagnosis associated with index visit (initial visit) and revisit.
DESIGN	Observational: Retrospective, Non-concurrent cohort study

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
Aside from the exposure of interest did the exposed and control groups start and finish with the same risk for the outcome?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or did statistical adjustments address the imbalance).	Yes. TABLE 1. The patients in the 2 study groups (tachycardic at discharge vs normal heart rate at discharge) were similar with respect to patient age, sex, race, and ethnicity. Factors that are commonly associated with tachycardia such as pain scores, medications, and underlying primary diagnosis were also similar
Were the circumstances and methods for detecting the outcome similar?	Yes. This was a retrospective chart review. Data that was electronically extracted from the electronic health records. Extracted variables included patient demographics, triage and discharge vital signs and the times that they were obtained, total number of pulse rate measurements during the encounter, medications that were administered, timing of medication administration, pain scores and time at which the pain score was obtained, billing diagnosis, and clinically important interventions performed if the patient had a revisit within 72 hours.
Was follow-up sufficiently complete?	Likely yes. This study was a retrospective chart review. 126,774 patients were enrolled in the study and 4,294 (3.4%) had a revisit to either the enrolled ED or urgent care centers within 72 hours. It is unknown if other patients revisited to facilities outside of the enrolled ED's or urgent cares centers or to their primary care providers. However, the authors state that their institution is the only free-standing children's hospital within a 100-mile radius with a large catchment area. It is likely that children requiring significant interventions would have likely either presented to or been transferred to their institution.

WHAT ARE THE RESULTS?

How strong is the association between exposure and outcome?

UNSCHEDULED REVISIT WITHIN 72 HOURS			
	REVISIT WITHIN 72 HOURS		
	YES	NO	
TACHYCARDIC	504	9,996	10,470
NOT TACHYCARDIC	3,790	112,514	116,304
	4,294	122,480	126,774

Prevalence: Tachycardia at D/C: 10,470/126,774 = 8.3%
Prevalence: Revisits within 72 hrs 4,294/126,774 = 3.4%

Unscheduled Revisits
Tachycardic: 504/10,470 = 4.8%
Not Tachycardic: 3790/116,304 = 3.3%

Risk Difference: 1.5%, 95% CI (1.1, 2.0%)
Relative Risk: 0.48/0.33 = 1.45, 95% CI (1.2, 1.5)

Regression Analysis: Age, race, sex, ethnicity, insurance type, location of visit, presence of fever or pain, and administration of tachycardia-inducing medications demonstrated were not independent predictors of unscheduled revisits for patients who were tachycardic at discharge.

Sensitivity Analysis: The primary results of the study did not change significantly if patients with vital signs within 30 minutes of discharge or if only ED patients were included in the analysis

Secondary Outcomes:

ANY CLINICALLY IMPORTANT INTERVENTIONS AT REVISIT			
	IMPORTANT INTERVENTION		
	YES	NO	
TACHYCARDIC	129	375	504
NOT TACHYCARDIC	931	2,859	3,790
	1,060	3,234	4,294

Prevalence: 1,060/4,294 = 24.7%

Clinically Important Interventions at Revisit
Tachycardic: 129/504 = 25.6%
Not Tachycardic: 931/3,790 = 24.6%
Risk Difference: 1%, 95% CI (-2.8, 5.2%)
Relative Risk: 1.04, 95% CI (0.9, 1.22)

2. Those who were tachycardic at discharge and had a revisit within 72 hours (compared to those who were not tachycardic at discharge and has a return visit) were more likely to require/have:

CLINICALLY IMPORTANT INTERVENTIONS AT REVISIT	
	RR (95% CI)
Supplemental oxygen	1.8 (1.1–2.9)
Respiratory medications and admission	2.0 (1.3–3.0)
Antibiotics and admission	1.5 (1.1–2.0)
Peripheral IV and admission	1.4 (1.1–1.7)
Tachycardic at revisit	3.1 (2.6–3.7)
GREEN = STATISTICALLY SIGNIFICANT, RED = NOT STATISTICALLY SIGNIFICANT	

3. Admission: No statistically significant difference in rate of admission on revisit between tachycardic and non-tachycardic children with a revisit.
Admission from ED: RR 1.1, 95% CI (0.9, 1.3)
Direct admission to hospital: RR 0.6, 95% CI (0.3, 1.3)

HOW PRECISE IS THE ESTIMATE OF THE RISK?

The confidence intervals for the risk differences and relative risks are provided above. They are relatively narrow given the studies large sample size.

For the primary outcome, the confidence interval for the risk difference does not include 0 and the confidence interval for the relative risk does not include 1. These indicate a statistically significant difference with the risk of revisits higher in the patients with tachycardia at discharge. The clinical significance of the difference is unclear

For the secondary outcome, the confidence interval for the risk difference does include 0 and the confidence interval for the relative risk does include 1. These indicate that there is not a statistically significant difference between tachycardia at discharge and the composite outcome of requiring a clinically important intervention at revisit.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Yes. The study patients were similar to the patients seen at both Bellevue and Tisch hospital with respect to their age, sex, ethnicity, and primary diagnosis. Our patient population would not necessarily return to our emergency departments as there are many of options for re-visit
Was follow-up sufficiently long?	Yes. The primary outcome of the study was a revisit to the ED or urgent care center within 72 hours of discharge. This time frame was selected based on investigator consensus and relevant literature. Additionally, return visit to the ED within 72 hours is often used as a benchmark for quality of care in the ED. It is also a seemingly appropriate time frame to associate the possible progression or change of a clinical status from one hospital visit to the next.
Is the exposure similar to what might occur in my patient?	Unclear. Discharging a patient who is tachycardic from the emergency department is a provider specific decision. At Tisch ED, it is required that every patient has a set of vital signs within 60 minutes prior to discharge home. At Bellevue, there is no standard to check vital signs prior to a patient's discharge home unless it is specifically requested.
What is the magnitude of the risk?	Those patients who were tachycardic at time of discharge were more likely to have a revisit within 72 hours than those who were not tachycardic at time of discharge (Relative Risk 1.45 (95% CI 1.2-1.5)). However, of those who had a revisit, the rate of clinically important interventions were similar among the two groups and the difference was not statistically significant (Relative Risk 1.04 (95% CI 0.9-1.0)). Those who were tachycardic at discharge and who had a revisit did however require supplemental oxygen, respiratory medications, antibiotics and admission, peripheral IV placement and admission, and were more likely to be tachycardic at revisit, than those who were not tachycardic at discharge from their initial visit.
Are there any benefits that offset the risks associated with exposure?	If a patient is tachycardic at the time of discharge from the emergency room, this could be secondary to a number of factors. The most common conditions associated with tachycardia are fever, pain, and anxiety (crying). While tachycardia is not considered a benefit, it is an expected response to a number of conditions. Based on the risk difference for the primary outcome (ARD = 1.5%) for every 67 patients (1/0.015) who are tachycardic at discharge 1 additional patient will have an unscheduled revisit within 72 hours.

CLINICAL BOTTOM LINE

BACKGROUND: Tachycardia is a very common abnormal vital sign in the Pediatric Emergency Department. Tachycardia can have numerous underlying causes including less concerning clinical states such as fever, pain, and anxiety but can also be a sign of impending cardiovascular decompensation which occurs in shock, sepsis, and cardiac dysfunction. This study aimed to determine if tachycardia at time of discharge from the Pediatric Emergency Department was a risk for revisit within 72 hours of discharge and if those who had a revisit required clinically important interventions.

CLINICAL QUESTION: In patients less than 19 years of age, is tachycardia at the time of discharge from the ED or urgent care center associated with increased risk of revisit within 72 hours or the receipt of clinically important interventions, or hospital admission on revisit?

DESIGN/RISK OF BIAS: This was a well-designed study with little risk of bias. The study was a retrospective cohort chart review. It used a large database with sample size of 126,774. The authors mention certain limitations of the study that could be expected of retrospective chart review. These included the possibility of interventions to address the tachycardia after the final pulse rate was recorded (therefore leaving the final pulse rate prior to discharge unknown and ultimately overestimating the number of patients discharged with tachycardia), the highly variable accepted thresholds for heart rate among practitioners, the fact that revisits within 72 hours may have occurred at location outside of their study sites, and that urgent care visits were included in their study. The study did not address that the need for clinically important interventions and hospital admission are often subjective decisions that are made at the discretion of the treating physician.

PRIMARY RESULTS: The primary outcome of the study was unscheduled revisits to either the emergency department or urgent care within 72 hours of discharge from the initial visit. 8.3% of all the studied patients (10,470/126,774) were tachycardic at time of discharge. Additionally, 3.4% (4,294/126,774) of patients (both tachycardic and not tachycardic at the time of discharge) had an unscheduled revisit within 72 hours of discharge. Of those who were tachycardic at discharge, 4.8% (504/10,470) had a revisit within 72 hours of discharge. Of those who were not tachycardic at discharge, 3.3% (3790/116,304) had a revisit within 72 hours. The relative risk (RR: 1.45 95% CI (1.2, 1.5)) and risk difference (1.5%, 95% CI (1.1, 2.0%)) for revisit between was statistically significant higher in those tachycardic at discharge. However. it is unclear if this 1.5% difference is clinically significant. The authors did not report what they considered to be a clinically significant difference.

The secondary outcome was the receipt of clinically important interventions at the revisit. 25.6% of patients who were tachycardic at discharge and who had a revisit within 72 hours of discharge received clinically important interventions. 24.6% of those who were not tachycardic at their index visit and who had a revisit within 72 hours received clinically important interventions. This difference was not statistically significant with a risk difference of 1%, 95% CI (-2.8, 5.2%). Those who were tachycardic at discharge and had a revisit within 72 hours were more likely to require supplemental oxygen, respiratory medications and admission, antibiotics and admission, intravenous placement and admission, and were more likely to be tachycardic at their revisit. There was no difference in the rate of admission on revisit between tachycardic and non-tachycardic patients with revisits.

APPLICABILITY: The results of this study can be applied to a wide variety of patients who are discharged from the Pediatric Emergency Department. In this study, the patient demographics, the factors that are commonly associated with tachycardia including pain, medications, and the underlying primary diagnosis, in addition to the clinical interventions used to manage various conditions are broadly seen and used across different clinical practices.

AUTHOR'S CONCLUSION: "In summary, in this large cohort of children treated during one year in pediatric acute care settings, discharge tachycardia was associated with an increased risk of revisit but was not associated with an increased risk of the composite outcome of receiving clinically important intervention at revisit. Given our study's retrospective nature, future prospective studies may uncover additional factors not fully examined here; however, given the size of our cohort, it is likely that screening for tachycardia at discharge is not the ideal method for identifying impending physiologic deterioration, and focused efforts at addressing all tachycardia before discharge may be unwarranted."

POTENTIAL IMPACT: Tachycardia in the Pediatric Emergency Department is a very common abnormal vital sign finding that often prolongs a patients' stay in the emergency department. Patient's often undergo additional testing to find the underlying cause of their tachycardia and to ensure that the tachycardia is not a sign of impending cardiovascular compromise. Often, an underlying cause is not identified and the physician is left with a feeling of unease discharging a patient home with an abnormal vital sign. This study demonstrated that tachycardia at time of discharge is associated with a 1.5% higher rate of revisits within 72 hours of discharge. Importantly, it demonstrated that those who were discharged with tachycardia and had a revisit, did not require more clinically important interventions or admissions than those who were not tachycardic at time of discharge and who also had a revisit.

This was a study with a large and diverse patient population that can be applied to most pediatric acute care settings. If applied, this study could lead to shorter emergency department visits, less testing, and provide the physician with a sense of reassurance that tachycardia, on its own at time of discharge, is not associated with a poor clinical outcome. Close follow up of these patients assured and clear return precaution should be provided.

INTRAVENOUS ONDANSETRON: QT INTERVAL PROLONGATION

Do pediatric patients receiving intravenous Ondansetron have an increase in their QTc when compared to their baseline QTc at the time of peak concentration and at 1 hour post administration?

Nicole Gerber M.D., Michael Mojica, M.D.
November 2016

Krammes SK, Jacobs T, Clark JM, Lutes RE.

EFFECT OF INTRAVENOUS ONDANSETRON ON THE QT INTERVAL OF PATIENTS' ELECTROCARDIOGRAMS.

Pediatr Emerg Care. 2016 Jun 2.
PubMed ID: 27261956

STUDY DEFINITIONS	
POPULATION	Inclusion: 6 months-18 years, intravenous Ondansetron for vomiting, nausea or inability to take oral fluids Exclusion: 1. Unable to perform EKG 2. History of arrhythmia including prolonged QT 3. History of congenital cardiac disease 4. Contraindication to receiving Ondansetron 5. Requiring fluid resuscitation for shock Setting: Single Children's hospital pediatric ED, 7/2012-3/2013
EXPOSURE	Intravenous Ondansetron 0.15 mg/kg (max of 4 mg or 8 mg at MD discretion)
NO EXPOSURE	Baseline EKG to determine the QTc prior to receiving Ondansetron
OUTCOME	Primary Outcome: QTc interval change from baseline to peak drug effect (3 min) Secondary Outcomes: QTc interval change from baseline to 1 hour after peak drug effect Clinically significant EKG changes
DESIGN	Prospective cohort study

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
Aside from the exposure of interest did the exposed and control groups start and finish with the same risk for the outcome?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or did statistical adjustments address the imbalance).	Not applicable. In this study, all of the patients served as their own controls. In table 1, it seems that all important baseline characteristics were recorded. About 50% of the patients were female, the age range was 1-18 years with a mean of 8.3 years, Ondansetron dosing ranged from 1.3-8 mg with a mean of 3.4 mg. The baseline QTc was 388-501 msec with a mean of 435 msec. They also discuss discharge diagnosis, with 69% of the patients diagnosed with gastroenteritis but a wide variety of other diagnoses including diabetic ketoacidosis.
Were the circumstances and methods for detecting the outcome similar?	Yes. All of the patients had a baseline EKG performed, were then given the dose of intravenous Ondansetron and then had two additional EKGs, one at the time of peak effect of the medication (3 minutes) and one at 60 minutes after the peak effect of the medication
Was follow-up sufficiently complete?	Yes. All 100 of the patients included in the analysis had all 3 of the EKGs performed. Follow up after ED discharge was not done.

WHAT ARE THE RESULTS?

How strong is the association between exposure and outcome?

Baseline QTc = 435 msec

Primary Outcome: Change QTc baseline to 3 minutes
Mean change: 3 msec
Standard deviation 16 msec
Range (-40 to 65) msec

Secondary Outcome: Change QTc baseline to 1 hour
Mean change: 3
Standard deviation 16 msec
Range (-43 to 45) msec.

62% increase in QTc (mean ↑12 msec, range 0-65 msec)
12% increase in QTc > 20 msec
4% increase in QTc to > 480 msec, All < 480 msec 1 hr.
1% increase QTc > 500 msec (503), 471 msec at 1 hour, no change in rhythm,

How precise is the estimate of the risk?

There is not enough information provided to determine a 95% confidence interval.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Likely. In table 1, about 50% were female, the age range was 1-18 years with a mean of 8 years and the mean dose of Ondansetron was 3.4 mg (1.3 – 8 mg). It would have been helpful to report and mean dose per kilogram. In terms of the discharge diagnoses, they also seem similar to what we use Zofran for: gastroenteritis/vomiting, infectious processes like Strep pharyngitis or Influenza, genitourinary complaints like UTI or nephrolithiasis and other diagnoses including closed head injury, seizure, migraine, or DM/DKA. The authors do not report demographic information for their patient population.
Was follow-up sufficiently long?	Yes. The medication peak effect is at 3 minutes after administration. The medication effect should be expected to diminish over time. These patients were measured at 1 hour after the peak. Because of natural variation in QTc in children, it would have been interesting if they calculated the QTc more than once at each time point, but not necessarily at a later time point.
Is the exposure similar to what might occur in my patient?	There are two differences. They sometimes use a maximum dose of 4 mg and sometimes 8 mg. They use only intravenous Ondansetron in this study, in our patients we typically use the oral route.
What is the magnitude of the risk?	The magnitude of the risk in this study was the mean change in QTc at 2 times after Ondansetron administration (see results). The use of this outcome assumes that those with an initially low QTc increase to the same extent as those with an initially high QTc. If those with an initially high QTc increased more this would have been important to report. A graph of initial QTc (X axis) versus change in QTc (Y-Axis) would have been helpful.
Are there any benefits that offset the risks associated with exposure?	Yes. Ondansetron has been found to be effective in improving the success of oral rehydration therapy in children with gastroenteritis.

CLINICAL BOTTOM LINE

BACKGROUND: In adult studies, Ondansetron has been associated with a statistically significant prolongation of the QTc interval that is typically asymptomatic and transient. However, there are few studies in pediatric patients despite the fact that Ondansetron use is increasing in the pediatric population and has been shown to improve success of oral rehydration in children with gastroenteritis. Ondansetron use is children is FDA approved for patients receiving chemotherapy and those who are post operative. Use for other indications is off-label

CLINICAL QUESTION: Do pediatric patients receiving intravenous Ondansetron have an increase in their QTc at the time of peak concentration and at 1-hour post administration when compared to their baseline QTc?

DESIGN/RISK OF BIAS: This was a well designed, prospective cohort study that included 100 pediatric patients. The were minimal validity concerns. These include those related to cohort studies in general, a small sample size (100) and the inherent variability in QTc intervals in children.

PRIMARY RESULTS: The primary outcome was change in QT interval at peak drug effect. The authors report their findings in terms of a mean change with a standard deviation and range. There was a 3 msec increase in QTc from baseline to peak onset (standard deviation 16 msec, range -40 – 65 msec). The was a 3 msec increase in QTc from peak to 1 hour (standard deviation 16 msec, range -43 – 55 msec). The American College of Cardiology suggests that medications are safe as long as the QTc isn't prolonged longer than 500 msec or increased by greater than 60 msec from baseline. However, the authors did not report their findings in terms of these guidelines. They did report that the prevalence of QTc over 480 at the peak effect of Ondansetron was 4% and all returned to < 480 msec at 1 hour. There was one patient in the study who had a peak QTc > 500 msec who was later found to have electrolyte abnormalities. No patient had a clinically significant change in their cardiac rhythm after medication administration.

APPLICABILITY: The patient population is likely similar to our population although no demographic information is reported. Other important considerations are that the maximum dosage of Ondansetron was not standardized (4 mg or 8 mg at provider discretion) and all of the patients in this study were given intravenous Ondansetron, whereas the oral route is most typically used in combination with oral rehydration in those with acute gastroenteritis.

AUTHOR'S CONCLUSION: "Our pilot study shows that ondansetron remains safe to use in previously healthy children with an acute illness of nausea, vomiting, or inability to take oral fluids. The minimal increase in QTc from baseline at peak effect and 1-hour post-peak effect leans toward statistical significance but with no or very minimal clinical significance. Those patients with a positive change in QTc showed a small mean increase of 12 milliseconds, which was statically significant. A larger prospective study should be conducted to confirm these findings."

POTENTIAL IMPACT: The authors describe this as a pilot study. Given the limitations of this study, it is unlikely to change individual practice standards, but may provide support to the continued use of Ondansetron off label for treatment of clinical conditions associated with nausea and vomiting in children. Care should be taken in administering Ondansetron with other medications (e.g. Azithromycin) or in patients with electrolyte abnormalities (e.g. hypocalcemia) that increase the QTc. The one patient in this study with a QTc > 500 msec at peak after Ondansetron had electrolyte abnormalities though no clinically significant change in cardiac rhy

CHILD PROTECTION

1. Abusive Head Trauma Decision Rule: Pediatrics 2016

CHILD PROTECTION:
ABUSIVE HEAD TRAUMA DECISION RULE

In pediatric patients between 1-12 months of age who present to the ED without a history of trauma but with symptoms associated with an increased risk of abusive head trauma do the clinical predictors included in the Pittsburgh Infant Brain Injury Score accurately identify patients with and without abusive head trauma?

Shweta Iyer, M.D., Alvira Shah, M.D.
May 2017

Berger RP, Fromkin J, Herman B, Pierce MC, Saladino RA, Flom L, Tyler-Kabara EC, McGinn T, Richichi R, Kochanek PM.

VALIDATION OF THE PITTSBURGH INFANT BRAIN INJURY SCORE FOR ABUSIVE HEAD TRAUMA.

Pediatrics. 2016 Jul;138(1).
PubMed ID: 27338699

STUDY DEFINITIONS	
POPULATION	Inclusion: 30-364 days, well-appearing, presented to the ED, temperature < 38.3°C, no history of trauma, symptom associated with increased risk of abusive head trauma including: ALTE, apnea, vomiting without diarrhea, seizure/seizure like activity, soft tissue swelling of the scalp, bruising and non-specific neurologic symptoms (lethargy, fussiness, poor feeding). Exclusion: Previous abnormal head CT Setting: Multicenter (3) Children's Hospital EDs, 10/2006-4/2014
RULE PARAMETERS	Clinical and laboratory parameters collected on a standardized data collection instrument. Included: history of present illness, past medical history, previous ED visits, results of laboratory and radiologic testing, neurologic and dermatologic examination findings, serum hemoglobin, head circumference, and discharge diagnoses. Socioeconomic status or social history were not collected.
REFERENCE STANDARD	Radiologic Classification: Normal, Equivocal, Abnormal (See Appendix) Cases: Abnormal neuroimaging at enrollment or during follow-up. Sub-classified as: Possible traumatic, Probable/Definite traumatic, Atraumatic Controls: Normal neuroimaging or no neuroimaging at enrollment or follow-up Abusive Head Trauma: Brain injury assessed by child protection team as due to definite or probable abuse (not including possible abuse).
OUTCOME	Decision rule characteristics Area under the receiver operating characteristic curve
DESIGN	Clinical Decision Rule: Prospective, Multicenter Validation

HOW SERIOUS WAS THE RISK OF BIAS?	
Were the patients chosen in an unbiased fashion and do they represent a wide spectrum of severity of disease?	Unclear. Clear inclusion and exclusion criteria were provided. Enrollment occurred by convenience sampling. The proportion of eligible patients enrolled was not provided. There is a possibility of sampling bias.
Was there a blinded assessment of the criterion standard for all patients?	Unclear. The child protection team's assessment of the likelihood of abusive head trauma as definitely or probably due to abuse served as the criterion standard for abusive head trauma. It is unlikely that they were blinded to the presence of the decision rule parameters in making their assessment. The inclusion of the rule parameters in determining the outcome could artificially improve the rule characteristics. Neuroimaging was interpreted by a clinical care and study neuro-radiologist. If a difference of interpretation occurred a pediatric neurosurgeon reviewed the images and consensus was reached. Only 61% of the patients without abusive head trauma had neuroimaging at enrollment of on follow up (possible verification bias).
Was there an explicit and accurate interpretation of the predictor variables and the actual rule without knowledge of the outcome?	Yes. Data was collected in prospectively prior to the results of imaging and prior to the assessment of the child protection team.
Was there 100% follow up of those enrolled?	Subjects were tracked by review of medical records for 6 months or up to 1 year of age, whichever came later. The proportion of patients without imaging or with initially normal imaging who were available for follow up was not presented.

WHAT ARE THE RESULTS?	
Demographic data	N = 1,040 (77% at primary center) Case: 214 (21%), Neuroimaging 99.5% enrolled, 0.5% f/u Control: 826 (79%), Neuroimaging 61% Mean age 4.7 months, 78% white Direct to ED (59%), office referral (30%), other hospital referral (10%) <u>Independent predictor of Abusive Head Trauma</u> Abnormal Dermatologic Exam Age ≥ 3 Months Head Circumference > 85th percentile Hemoglobin < 11.2 gm/dl
How well did the rule correctly identify patients <u>with</u> the primary outcome? How precise was this measurement? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)	Based on 862 (83%) patients with complete data <u>Area Under the Receiver Operating Characteristic Curve</u> 0.83, 95% CI (0.80, 0.86) <u>Identification of Abnormal Imaging (Rule Score)</u> Sensitivity (2): 93% (89.0, 96.6%) Predictive Value Negative Rule (< 2): 96% (93.6, 97.9%)
How well did the rule correctly identify patients <u>without</u> the primary outcome? How precise was this measurement? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)	Based on 862 (83%) patients with complete data <u>Identification of Abnormal Imaging</u> Specificity (2): 53%, 95%CI (49.3,57.1%) Predictive Value Positive Rule (≥ 2): 39% (34.8, 43.6%)
How would use of the rule impact resource utilization?	The proportion of infants with neuroimaging using the Pittsburgh Infant Brain Injury Score (55%) is similar to that in the study population (59%). The author state that the goal was not to decrease the number of infants who undergo head CTs but to target head CTs to those infants who are most likely to have a positive result.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (See Appendix)	☐ I ☐ II ☐ III ■ IV Unclear. This study is described as a validation of a decision rule but is in fact a prospective, multicenter re-derivation of a rule. Two variables were eliminated from the original rule and the cut-off point for an additional variable was changed. A separate internal validation set was not presented. This is a level IV rule. Level IV rules have been derived only or validated only in split samples, large retrospective databases or by statistical methods. A level IV rule requires further validation before it can be applied clinically.
Does the rule make clinical sense?	Yes and No. The 4 predictors included in the rule are clinically associated with a risk of abnormal neuroimaging but not specifically associated with a risk of abusive head trauma.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. 3 of the 4 rule predictors are objective: age ≥ 3 months, head circumference > 85th percentile and hemoglobin < 11.2 gm/dl. The 4th parameter, which is the one with the greatest weight (2 points) “abnormality on dermatologic exam” would need to be accompanied by a decision support tool such as in Figure 1 to precisely define the predictor. Inter-rater reliability of this predictor was not presented.
Is the rule applicable to the patients in my practice?	Unclear. Many infants present with vague signs and symptoms for which intracranial injury should be considered. The authors indicate that the prevalence of abusive head trauma was higher than expected. A population with a lower prevalence of abusive head trauma would have a lower posttest probability of disease (a lower predictive value of a positive rule and a higher predictive value of a negative rule) than seen in the study.
Will the rule results change my management strategy?	No. Not a present. It requires further validation.
What are the benefits of applying the rule to my patients?	The potential benefit of a validated rule that demonstrated impact would be to target head CT use to those at highest risk limiting unnecessary head CT’s and reducing radiation exposure.
What are the risks of applying the rule to my patients?	The potential risk of the applying the rule is missing a patient with abnormal neuroimaging due to abusive head trauma. The lower limit of the 95% confidence interval for the predictive value of a negative rule was 93.6%. This indicates that 6.4% of patients with a negative rule could have abnormal neuroimaging. In this study 50% of those with abnormal neuroimaging had probable or definite abusive head trauma. Missing these patients can be life threatening.

CLINICAL BOTTOM LINE

BACKGROUND: Abusive head trauma is the leading cause of death from child abuse and the leading cause of death from traumatic brain injury. Identification of clinically important traumatic brain injury is essential. The PECARN head trauma rule for children less than 2 years of age includes 6 predictors (PECARN, Lancet, 2009, PubMed ID: 19758692). The predictors of "acting normally as per parents" and "a high-risk mechanism of injury" may be unreliable in infants with abusive head trauma. Because symptoms of abusive head trauma are non-specific a high percentage of patients are seen by physicians prior to a definitive diagnosis. The Pittsburgh Infant Brain Injury Score was retrospectively derived from 187 infants (37 with abusive head trauma) who presented to a single tertiary care children's hospital. Five predictor variables were identified: age ≥ 3 months, head circumference percentile > 90th percentile, a serum hemoglobin <11.2 g/dl, an abnormality on neurologic or dermatologic examination, and a previous emergency department (ED) visit for a high-risk symptom. The receiver operator characteristic (ROC) curve had an area under the curve of 0.87, 95% CI (0.80, 0.95).

CLINICAL QUESTION: In pediatric patients between 1-12 months of age who present to the ED without a history of trauma but with symptoms associated with an increased risk of abusive head trauma do the clinical predictors included in the Pittsburgh Infant Brain Injury Score accurately identify patients with and without abusive head trauma?

DESIGN/RISK OF BIAS: The study is a multicenter, prospective validation of the Pittsburgh Infant Brain Injury Score. In included 1,040 patients of which 214 had abnormal neuroimaging. 51% (109/214) of those with abnormal neuroimaging were ultimately considered to have a probable or definite abusive head trauma by the child protection team.

This study is described as a validation of a previously derived rule but is in fact a re-derivation of the rule. Two previous parameters, previous ED visit for a high-risk symptom and an abnormal neurologic exam were not included in the new rule. In addition, the cutoff point for head circumference was decreased from > 90% to > 85%. The rule is described as a score for the identification of abusive head trauma yet the rule characteristics are presented for the identification of abnormal neuroimaging. 51% (109/214) with abnormal brain imaging were considered to have abusive head trauma. Rule characteristics for the identification of abusive head trauma are not presented.

Other validity concerns include the possibility of selection bias. The study was a convenience sample without a description of missed patients. It is not clear if referred and transferred patients were sent because of concern for abusive head trauma and only 80% of patients had sufficient data to be included in the calculation of the rule characteristics. There also is a possibility of verification bias. Not all patients had imaging and the proportion of patients available for follow up was not reported.

PRIMARY RESULTS: The analysis identified 4 independent, weighted predictors of abnormal neuroimaging. The overall performance of the rule was good as indicated by an area under the receiver operating characteristic curve of AUC 0.83, 95% CI (0.80, 0.86). The rule correctly identified those with abnormal neuroimaging the majority of the time (Sensitivity (Score of 2): 93% (89.0, 96.6%, Predictive Value of a Negative Rule (Score < 2): 96% (93.6, 97.9%). The rule was not as accurate in identifying those without abnormal neuroimaging (Specificity (Score of 2): 53%, 95%CI (49.3,57.1%), Predictive Value of a Positive Rule (Score ≥2): 39% (34.8, 43.6%)). Use of the rule in the study population would not have decreased the rate of neuroimaging.

The author state that the goal was not to decrease the number of infants who undergo head CTs but to target head CTs to those infants who are most likely to have a positive result.

PITTSBURGH INFANT BRAIN INJURY SCORE	SCORE
Abnormal Dermatologic Exam	2
Age ≥ 3 Months	1
Head Circumference > 85th percentile	1
Hemoglobin < 11.2 gm/dl	1

APPLICABILITY: This study is described as a validation of a previously derived decision rule but is in fact a re-derivation of the rule. Two previous parameters, previous ED visit for a high-risk system and neurologic exam were excluded from the rule. In addition, the cutoff for head circumference was decreased from > 90% to > 85%. An internal validation analysis was not included. This is a level IV rule. It is a rule that has been derived only or validated only in split samples, large retrospective databases or by statistical methods. A level IV rule requires further validation before it can be applied clinically.

It is essential to remember that the Pittsburgh Infant Brain Injury Score was designed to be used in well-appearing infants in whom brain injury may not be part of the initial differential diagnosis. The rule is not generalizable to patients in which there is a high suspicion of non-accidental trauma. In addition, the predictor “abnormal dermatologic exam” is somewhat subjective and no measure of inter-rater reliability was presented.

AUTHOR’S CONCLUSION: “In conclusion, our study suggests that Pittsburgh Infant Brain Injury Score can identify infants at increased risk for brain injury who should undergo neuroimaging. As with all clinical prediction rules, implementation analysis is essential before incorporating Pittsburgh Infant Brain Injury Score into clinical practice to determine whether Pittsburgh Infant Brain Injury Score improves identification of abusive head trauma and/or changes the use of neuroimaging to screen for brain injury in the emergency department setting.”

POTENTIAL IMPACT: The concept that nonspecific symptoms in an infant can be due to abusive head trauma is important to remember. This study represents a first step in the development of a decision rule to identify infants without a history of head trauma but with symptoms that may be related to head trauma who are likely to have abnormal imaging. Several limitations need to be addressed before it can be adopted clinically.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

APPENDIX: TRAUMATIC BRAIN INJURY IMAGING CLASSIFICATION

NEUROIMAGING CLASSIFICATION	
NORMAL	
Clinically insignificant abnormality defined as an incidental finding that does not result in any follow-up or is unrelated to the clinical presentation. These include the following	
1	Mild prominence/enlargement or asymmetry of ventricles
2	Prominent suture(s) or vascular grooves
3	Enlarged posterior fossa
4	Plagiocephaly
5	Mild volume loss
6	Resolving cephalohematoma[a]
7	Small cysts
8	Isolated soft tissue swelling
9	Sequelae of birth trauma (e.g., periventricular leukomalacia, intraventricular hemosiderin, incidental finding of posterior fossa subdural)
10	Benign extra-axial fluid of infancy
EQUIVOCAL	
Defined as an interpretation prefaced by “possible,” “probable,” “suspicious for,” “cannot rule out,” or “versus.”	
All findings initially assessed as equivocal were subsequently categorized as “normal/clinically insignificant abnormality” or “abnormal” based on clinical testing (e.g., additional CTs or MRIs) occurring during the follow-up period.	
If no follow-up testing was performed during the follow-up period, then the equivocal finding was considered to be “normal/clinically insignificant.”	
ABNORMAL	
PROBABLE/DEFINITE TRAUMA[C]	
1	Most cases of acute extra-axial hemorrhage
2	Skull fracture/skull fracture with underlying intracranial hemorrhage
3	Intraparenchymal contusion/hemorrhage
POSSIBLE TRAUMA	
1	Cases of acute extra-axial hemorrhage with atypical clinical circumstance (e.g., underlying bleeding disorder, with moderate/severe volume loss, with significant extra-axial spaces)
2	Chronic subdural hemorrhage (without acute subdural hemorrhage)
3	Moderate or severe volume loss
4	Laminar necrosis
5	Encephalomalacia
6	Cerebral edema (vasogenic or cytotoxic/stroke): localized or diffuse
NOT TRAUMA	
1	Mass lesions/tumors/cavernoma
2	Hydrocephalus
3	Craniosynostosis/skeletal dysplasias/other bony abnormalities
4	Any type of cortical dysplasia
5	Miscellaneous including tuberous sclerosis, Dandy-Walker malformation, arteriovenous

[A] Can be traumatic, but is so commonly related to birth trauma in infants that it would not influence clinical care.
[B] Can be traumatic, but in the absence of a skull fracture or other evidence of trauma, it is far more likely to be due to positioning or a normal variant and would not influence clinical care.
[C] All cases of abusive head trauma were classified as probable/definite trauma.

DERMATOLOGY

1. Abscess: Packing: Acad Emerg Med. 2009
2. Abscess: Antibiotics (Adults): N Engl J Med. 2016
3. Abscess: Antibiotics (Pediatrics): Ann Emerg Med. 2010
4. Abscess: Antibiotics (Meta-analysis): Annals EM. 2019
5. Abscess: Loop Drainage Technique: AM J EM 2017

ABSCESS INCISION & DRAINAGE: PACKING

In patients with a simple cutaneous abscess does incision and drainage without wound packing when compared to incision and drainage with wound packing result in a similar rate of complications and improved post procedural pain?

David Kessler, M.D., Jeffrey Fine. M.D
June, 2009

O'Malley GF, Dominici P, Giraldo P, Aguilera E, Verma M, Lares C, Burger P, Williams E.

ROUTINE PACKING OF SIMPLE CUTANEOUS ABSCESSES IS PAINFUL AND PROBABLY UNNECESSARY

Acad Emerg Med. 2009 May;16(5):470-3
PubMed ID: 19388915

STUDY DEFINITIONS	
POPULATION	Inclusion: ≥ 18 years, cutaneous abscess (trunk or extremities), requiring incision and drainage Exclusion: Abscess: > 5 cm, abscesses on the face, neck, scalp, hands, feet, perianal, rectal, or genital areas; hidradenitis or pilonidal abscesses Comorbid medical conditions: Pregnancy, diabetes, HIV, any malignancy, chronic steroid use, immunosuppressive states, sickle cell disease, sarcoidosis Allergies: Allergy to sulfa or hypersensitivity to trimethoprim-sulfamethoxazole Procedure: Need for procedural sedation or supplemental treatment, intravenous antibiotics or surgical consultation Follow-up: Inability to return for 48-hour follow-up. Setting: Single, Academic Medical Center ED, 2/2006-8/2006
INTERVENTION	Wound incision and drainage without abscess packing.
CONTROL	Wound incision and drainage with abscess packing (1/4 inch non–iodophor-impregnated gauze)
CO-INTERVENTION	1. Standardized approach to incision and drainage: Abscess area cleaned with chlorhexidine solution, anesthetized with 1% bicarbonate-buffered lidocaine, incised with a No. 10 surgical scalpel, aerobic cultures collected 2. Not standardized: Irrigated with normal saline, and used a cotton-tipped applicator to break up loculated areas within the abscess cavity. 3. Antibiotics: Trimethoprim-Sulfamethoxazole: 800 mg/160 mg Q12H 4. Analgesics: Oxycodone/Acetaminophen: 5 mg/325 mg Q4H PRN pain and Ibuprofen: 600 mg Q4H PRN pain. 5. Follow-up: ED at 48 hours, by phone at 10-15 days
OUTCOME	Primary Outcome: Need for intervention at 48 hours: 1. Extension of the previous incision 2. Further probing to break up loculations 3. Irrigation 4. Packing the wound 5. Change of initial antibiotics 6. Need for surgical evaluation 7. Admission to the hospital 8. Need for another (second) follow-up visit to the ED. Secondary Outcomes: Description of pain, amount of pain medication over 48-hours. Degree of erythema, induration, fluctuance.
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes, the groups were randomized onsite using an online random number generator.
Was randomization concealed?	Randomization was not concealed from treating physicians at the first visit.
Were patients in the study groups similar with respect to known prognostic factors?	Patients were similar regarding sex, age and ethnicity It would have been helpful to present the size, location and MRSA status of lesion as well are the area of erythema, depth and presence of cellulitis.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Randomization was not concealed from treating physicians at the first visit. Outcome assessors at 48 hours were blind to group allocation.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	14/48 (29%) patients did not follow-up. 11 in no packing group and 3 in the packing group. Phone calls were made to 10 of 11 in the no packing group and 1 of 3 in packing group. 3 patients were lost to follow-up. 75% were called at 10-15 days for long-term follow-up
Were patients analyzed in the groups to which they were randomized?	Yes. But only 56% in non-packed group and 87% in packed group returned for a 48-hour visit.
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 48 (Packing: 23, No Packing: 25), MRSA 60%

<u>Complications: Need for Intervention at 48 hours</u>
(Defined as: irrigation, repeat I&D, need for f/u)
Absolute Risk: No Packing: 5/25 (20%)
Absolute Risk: Packing: 4/23 (17.4%)
Absolute Risk Difference: 2.6% (-20, 24.4%)

<u>Mean Difference: VAS Pain Scale (Packing –No Packing)</u>
Pre: 10.25 (-7.5, 27.9) mm
Post: 23.8 (5, 42) mm
48 hours: 16.4 (1.6, 31.2) mm

<u>Analgesics: Oxycodone/Acetaminophen</u>
Packing (3.1) vs No Packing (0.91) pills in 48hrs
Mean Difference: 2.1 pills (0.2, 4.1 pills)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The small sample size resulted in a very wide confidence interval for the risk difference of the primary outcome.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Yes. The study patients were similar to the adolescent and young adults seen in our ED. However, younger patients were excluded.
Were all patient important outcomes considered?	They did not assess recurrence past 15 days and did not include the number of required follow-up visits as an outcome measure. A cost-effective analysis of both approaches would be interesting as well.
Are the likely treatment benefits worth the potential harm and costs?	There was more pain in the packed group post-procedure and at 48 hours. The magnitude of the difference is of unclear clinical significance. The packed group also used a mean of 2 more narcotic pills in 48 hours, which is of questionable clinical relevance. They did not find any difference in complications at 48 hours. Follow-up was poor for the primary outcome, and long-term follow-up was not complete. It is unclear if the potential risks outweigh the minimal benefit found in pain control.

CLINICAL BOTTOM LINE

BACKGROUND: Traditionally, abscesses are managed by incision and drained and packing of the wound cavity. Packing is thought to promote wound drainage and prevent premature closure of the wound. Packing could potentially increase patient pain and result in a greater number of follow-up visits. The purpose of this pilot was to determine whether packing a simple cutaneous abscess after incision and drainage confers any benefit with regards to pain and complications in a healthy adult population.

CLINICAL QUESTION: In patients with a simple cutaneous abscess does incision and drainage without wound packing result in a similar rate of complications and improved post procedural pain when compared to incision and drainage with wound packing?

DESIGN/VALIDITY: This randomized clinical trial included 48 patients. The primary validity concern is the small number of patients included in the trial. In addition, approximately a third of the patients did not return for follow up at 48 hours and those not returning were disproportionately in the no packing group. The study also used a composite primary outcome with some of the components of questionable relevance. For example, 3 of 9 of those requiring an intervention at 48 hours required additional wound irrigation and 1 requiring a change in antibiotics based on culture results.

PRIMARY RESULTS: There was no statistically significant difference between the packing group and no packing in those requiring an intervention at the 48 hour re-visit (No Packing: 5/25 (20%) Packing: 4/23 (17.4%), Difference: 2.6% (-20, 24.4%)). The packing group had more pain immediately post procedure and at 48 hours and took more narcotics than those in the no packing group though the magnitude of the difference in the pain outcomes is of unclear clinical significance

APPLICABILITY: As the authors conclude, the results of this small pilot study cannot be generalized.

AUTHOR'S CONCLUSION: "Although only a pilot study of safety, our data demonstrate that wound packing for simple cutaneous abscesses is painful and may be unnecessary."

POTENTIAL IMPACT: The study had a small sample size and a number of validity concerns. It should not be used to change current practice but could serve as a pilot for further study.

ABSCESS INCISION & DRAINAGE: ANTIBIOTICS (ADULTS)

In patients presenting to the emergency room with an uncomplicated cutaneous abscess requiring incision and drainage, is treatment with antibiotics (Trimethoprim-Sulfamethoxazole) superior to No Antibiotics (Placebo) in reducing treatment failures?

Kelsey Fawcett, MD., Alvira Shah, MD.
July 2016

Talan DA, Mower WR, Krishnadasan A,
Abrahamian FM, Lovecchio F, Karras DJ, Steele MT,
Rothman RE, Hoagland R, Moran GJ.

TRIMETHOPRIM-SULFAMETHOXAZOLE VERSUS PLACEBO FOR UNCOMPLICATED SKIN ABSCESS

N Engl J Med. 2016 Mar 3;374(9):823-32.,
PubMed ID: 26962903

STUDY DEFINITIONS	
POPULATION	Inclusion: > 12 years, suspected abscess based on physical exam or examination and ultrasound, purulent material on surgical exploration, < 1 week duration, ≥ 2 centimeters, intended for outpatient treatment. Exclusion: Indwelling device, suspected osteomyelitis or septic arthritis, diabetic foot, decubitus or ischemic ulcer, mammalian bite, wound with organic foreign body, infection of another organ system/site, perirectal, perineal, or paronychial location, intravenous drug use within previous month and fever, underlying skin condition, long-term care residence, incarceration, immunodeficiency, creatinine clearance < 50mL/min, cardiac condition with risk of endocarditis, allergy or intolerance to TMP-SMX, taking warfarin, phenytoin, or methotrexate, known G-6-PF or folic acid deficiency, pregnant or lactating, TMP-SMX treatment within 24 hours, concurrent treatment with topical or systemic antibiotic, or enrolled in the study within 12 weeks. Setting: Multicenter (5) U.S. Emergency Departments), 4/2009-4/2013
INTERVENTION	Trimethoprim-Sulfamethoxazole 320mg-1600mg BID for 7 days
CONTROL	Placebo x 7 days
CO-INTERVENTIONS	Abscess incision and draining (all personnel underwent standardized training) Study medication or placebo was provided for the patient
OUTCOME	Primary Outcome: Clinical failure 1. 3-4 days: Fever (attributable to the infection), Increase in the maximal dimension of erythema by > 25%, worsening of wound swelling, tenderness 2. 8-10 days: Fever, no decrease in erythema from baseline, no decrease in swelling or tenderness 3. 14-21 day: Fever or more than minimal erythema, swelling, or tenderness 4. Withdrew from the trial, lost to follow-up before final classification, had missing or unassigned outcomes Secondary Outcomes: 1. Composite cure: Resolution of all symptoms and signs of infection, or improvement such that no additional antibiotic therapy or surgical drainage procedure necessary 2. Changes in erythema size, the presence of swelling or induration and tenderness, 3. Invasive infections: Sepsis, bacteremia, endocarditis, osteomyelitis, septic arthritis, necrotizing fasciitis, or pneumonia), 4. Skin infections at the same or different site 5. Hospitalizations 6. Similar infections in household contacts 7. Days missed from normal activities, work or school, 8. Days analgesics used.
DESIGN	Interventional: Randomized clinical trial

ARE THE RESULTS VALID?

DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. The patients were randomized using web-based randomization in a 1:1 ratio to receive a 7 day course of either TMP-SMX (4 single strength pills, each containing 80 mg of TMP and 400 mg of SMX to be taken twice daily) or placebo (4 pills containing microcrystalline-cellulose to be taken twice daily)
Was randomization concealed?	Likely Yes. This study had few risks to bias the randomization process. While not explicitly stated, randomization into the 2 study groups occurred offsite and the study intervention (TMP-SMX) and control (Placebo) were in identical packaging.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. See Table 2. The patients in the 2 study groups had similar prognostic factors. 7-8% of each group had history of MRSA infection in the past (placing them at higher risk for repeat MRSA infection in the future) and approximately 11% of the patients in both groups were known diabetics (placing them at higher risk for skin infections). Abscess characteristics were similar between the treatment and the placebo groups including abscess size (length, width, depth) and the amount surrounding erythema. 43.5% of patients in the treatment group and 47.2% of patients in the placebo group had positive MRSA cultures from the abscess. It was not reported if patients had cellulitis in addition to an abscess.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The initial treating physician, the patient and the physician assessing outcomes were blinded to the study group
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDY'S CONCLUSION?	
Was follow-up complete?	In the modified intention to treat 1 analysis 630/636 (99%) were included in the TMP-SMX group and 617/629 (98%) were included in the Placebo group. In the per-protocol analysis 524/636 (82%) were included in the TMP-SMX group and 533/629 (85%) were included in the Placebo group.
Were patients analyzed in the groups to which they were randomized?	Yes. The authors completed two types of intention to treat analysis as well as a per protocol analysis. See Figure 1: Consort Diagram and Table 1 for study population definitions
Was the trial stopped early	No, the trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

MODIFIED INTENTION TO TREAT-1 GROUP

	CURE	NO CURE	
TMP-SMX	507	123	630
PLACEBO	454	163	617
	961	286	1247

Primary Outcome: Clinical Cure at the Test of Cure Visit

Absolute Risk (Clinical Cure)
Absolute Risk: TMP-SMX Group: 507/630 = 80.5%
Absolute Risk: Placebo Group: 454/617 = 73.6%
Absolute Risk Difference: (AR Placebo – AR TMP-SMX)
= 73.6% - 80.5% = -6.9%, 95% CI (-2.1, -11.7).
Patients in the TMP-SMX group were 6.9% more likely to have clinical cure at test of cure visit. This was a statistically significant difference. The authors specified a 7.5% difference to be clinically significant in the sample size determination

PER PROTOCOL GROUP

	CURE	NO CURE	
TMP-SMX	487	37	524
PLACEBO	457	76	533
	944	113	1,057

Absolute Risk (Clinical Cure)
Absolute Risk: TMP-SMX Group: 487/524 = 92.9%
Absolute Risk: Placebo Group: 457/533 = 85.7%
Absolute Risk Difference: (AR Placebo – AR TMP-SMX)
= 85.7% - 92.9%= - 7.2%, 95% CI, (-3.2, -11.2)
Patients in the TMP-SMX group were 7.2% more likely to have clinical cure at the test of cure visit. This was a statistically significant difference.
(Note: Risk difference: PP (7.2%) was similar to ITT (6.9%)

Secondary Outcomes (Per-Protocol Group):
Adverse Events: Most commonly involved gastrointestinal system. No treatment-associated serious or life-threatening adverse events occurred. One death in each group. Neither considered related to the TMP-SMX or the placebo.

	TMP-SMX	NO ANTIBIOTICS
Surgical drainage procedures*	3.4 %	8.6 %
Invasive infections	0.4 %	0.4 %
Infection at same or different site*	3.1 %	10.3%
Infection in household contacts*	1.7 %	4.1 %
*Statistically significant difference		

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?
For the per protocol group, the estimate of the treatment effect was quite precise. The study had a large N (1,057) and the confidence interval was narrow (3.2-11.2).

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	The patients in this study were similar to our patient population at Bellevue with a few exceptions. This study included adults with an average age of 35 years. It also included 11% of patients with diabetes. This is not similar to our pediatric patients with abscesses. We do, however, see a large amount of skin abscesses requiring incision and drainage. Our patient population also has a high incidence of MRSA which was represented in this study.
Were all clinically important outcomes considered?	Yes, all clinically important outcomes were addressed in this study and included repeat surgical incision and drainage, worsening infection, and invasive infections.
Are the likely treatment benefits worth the potential harm and costs?	Per Protocol Group: NNT = 1/ARD = 1/0.072 = 13.8 You would need to treat 13.8 patients with TMP-SMX to have 1 additional clinical cure of post incision and drainage at the test of cure visit when compared to placebo. Potential risks include an increase in bacterial resistance and rare but serious side effects of sulfa drugs such as Steven's Johnson syndrome.

CLINICAL BOTTOM LINE

BACKGROUND: Skin abscesses and soft tissue infections are common reasons to present to the emergency department. The incidence of skin abscesses has increased with the emergence of Methicillin Resistant Staph Aureus (MRSA). Traditionally, it has always been thought that incision and drainage of an abscess was the best method to achieve clinical cure. However, significant controversy surrounding the additional benefit of antibiotic use still exists among practitioners. Those who designed this study hypothesized that the cure rate among participants with a cutaneous abscess that was drained, would be greater in those treated with TMP-SMX than those treated with placebo.

CLINICAL QUESTION: In patients presenting to the emergency room with an uncomplicated cutaneous abscess requiring incision and drainage, is treatment with antibiotics (Trimethoprim-Sulfamethoxazole) superior to No Antibiotics (Placebo) in reducing treatment failures?

DESIGN/RISK OF BIAS: This study was a multi-center, double blind, randomized control trial, which aimed to determine if antibiotic therapy following incision and drainage of skin abscesses resulted in more rapid clinical cure, less incidence of abscess recurrence, and less need for further incision and drainage. Both the treating physician and the patient were blinded to the intervention being used (TMP-SMX vs Placebo). All patients who were included in the study had simple skin abscesses and were treated with either TMP-SMX or Placebo for 7 days following incision and drainage. Antibiotic selection of TMP-SMX was used to cover the most common bacteria found in uncomplicated skin abscesses: methicillin resistant staph aureus and methicillin sensitive staph aureus.

This was a well-designed study with few risks of biases. It included 1,265 patients with uncomplicated abscesses in the primary modified intention to treat analysis. Patients were followed up on a regular basis (day 3-4, day 8-10, day 14-21) to assess medication compliance. The primary outcome was clinical cure of the abscess at the test-of-cure visit (day 7-14). To reduce the risk of bias, inter-observer agreement (kappa) was assessed at the follow up visit. Additionally, standardized physical exam criteria for clinical failure at the test of cure visit were defined before the initiation of the trial, thus reducing the risk of subjective bias.

PRIMARY OUTCOME: The absolute risk of clinical cure in those patients treated with TMP-SMX post incision and drainage of cutaneous abscess in the intention to treat analysis was 80.5%. In comparison, the absolute risk in those patients treated with Placebo post incision drainage was 73.6%. The absolute risk difference between the two groups was 6.9%, 95% CI (2.1, 11.7%). While this does demonstrate a statistically significant difference between the two groups, this number does not meet the criteria for clinically significant difference of 7.5%, which was established from their power analysis. The number needed to treat in the per protocol group is 13.8. You would need to treat 13.8 patients with TMP-SMX to have 1 additional clinical cure post incision and drainage at the test of cure visit when compared to placebo. There was a statistically significant decrease in the secondary outcomes of: requiring an additional surgical drainage procedure, infections at the same or different site and infections in household contacts in the TMP-SMX group.

APPLICABILITY: Uncomplicated cutaneous abscess is a common reason for presentation to our pediatric emergency department, and for that reason this study is applicable to our patient population. One concern with this study, however, is that they included patients for which the current guidelines would recommend antibiotic use. This includes those a greater risk of infections (patients with diabetes and chronic skin conditions) and those with surrounding cellulitis (the area of erythema surrounding the abscess was on average 7.0 cm or 4.5 cm larger than the abscess). Inclusion of these patients would bias the study towards the benefit of antibiotics.

AUTHORS CONCLUSIONS: “In settings in which MRSA was prevalent, trimethoprim–sulfamethoxazole treatment resulted in a higher cure rate among patients with a drained cutaneous abscess than placebo.”

POTENTIAL IMPACT: It is difficult to determine whether the addition of antibiotics following incision and drainage of a simple skin abscess without surrounding cellulitis or high-risk conditions would be beneficial from the results presented. A sub-analysis excluding these high-risk patients would be helpful. The use of TMP-SMX, while commonly prescribed for MRSA infections, has been associated with C. Difficile colitis, renal and electrolyte problems, Steven’s-Johnson Syndrome, and its overuse can lead to microbial resistance.

This study, while perhaps not strong support for the use of antibiotics post incision and drainage of uncomplicated cutaneous abscesses, suggests that those with surrounding cellulitis may benefit from antibiotics, and that each patient should be treated on an individual basis depending on their clinical presentation and risk status.

ABSCESS INCISION & DRAINAGE: ANTIBIOTICS (PEDIATRICS)

In children from 3 months to 18 years of age who undergo incision and drainage of a cutaneous abscess, is treatment without antibiotics non-inferior to treatment with antibiotics in reducing treatment failures?

Carrie Danziger, M.D., Adriana Manikian, M.D.
July 2010

Duong M, Markwell S, Peter J, Barenkamp S.

RANDOMIZED, CONTROLLED TRIAL OF ANTIBIOTICS IN THE MANAGEMENT OF COMMUNITY-ACQUIRED SKIN ABSCESSES IN THE PEDIATRIC PATIENT

Ann Emerg Med. 2010 May;55(5):401-7.
PubMed ID: 19409657

STUDY DEFINITIONS	
POPULATION	Inclusion: 3 months-18 years, cutaneous abscess, non-toxic, temperature < 38.4°C. Abscesses diagnosed clinically and by bedside ultrasonography. Diagnostic criteria (all the following): 1. Onset within 1 week 2. Fluctuance 3. Erythema 4. Induration 5. Tenderness 6. With or without purulent drainage. Comprehend English sufficiently to provide consent and assent Exclusion: 1. Chronic health problems (e.g. diabetes) 2. Immunosuppressive medications (e.g. steroids) 3. Antibiotics currently or within 1 week 4. Contraindication to Trimethoprim-Sulfamethoxazole. 5. Superficial skin infections (e.g. folliculitis) Setting: Single Children's Hospital ED, 6/2006-2/2008
INTERVENTION	Trimethoprim-Sulfamethoxazole: 10-12 mg trimethoprim/kg/day divided into 2 doses, maximum 160 mg trimethoprim/dose for 10 days
CONTROL	Placebo: Maalox/tonic water, resembled antibiotic in color, texture, and taste.
CO-INTERVENTIONS	Procedure: Overlying skin cleaned with 10% povidone-iodine. # 11 blade used for incision, probed for loculations, irrigated with normal saline, cultures obtained Physician Discretion: Local anesthetic, sedation, incision size, wound packing Homecare Instructions: Remove gauze packing (if used), at 24 hours, warm water soaks ≥ twice a day, cover with gauge layer with taping at the edges. Avoid using: topical antibiotics, hydrogen peroxide, alcohol, or betadine Telephone follow-up: 2-3 days, 10-14 days, 90 days Clinical follow-up: 10-14-day
OUTCOME	Primary Outcome: 1. Clinical resolution: absence of erythema, warmth, induration, fluctuance, tenderness, and drainage at the 10-day follow-up. 2. Treatment failure: a. Any above signs or symptoms at 10-days b. Worsening signs or symptoms before 10-days requiring further surgical drainage, change in medication, admission for intravenous antibiotics. 3. New lesions ≤ 5 cm from the original abscess site Secondary Outcomes: 1. New lesions at a different site (> 5 cm from original abscess) on day 10 clinical follow-up, self-report or 3-month telephone follow-up. 2. Spread to household contacts by report at the 10-day and 3 month follow-up 3. Adverse effects from the medications at the 10-day follow-up 4. Compliance: > 50% of the medication taken
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS	
Were patients randomized?	Yes. Patients were computer randomized in permuted blocks of 50.
Was randomization concealed?	Yes. The inpatient pharmacist generated the randomization sequence, assigned the groups, and prepared, stored, and dispensed the medication. We assume that randomization was concealed because the clinicians had no role in the allocation though this was not explicitly stated.
Were patients in the study groups similar with respect to known prognostic factors?	Table 1. No statistically significant differences between the two groups for patient or abscess characteristics. The Placebo group had a higher rate of prior skin abscess (47% vs 34%) and less wound packing (70% vs. 82%) though these difference were not statistically significant.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Patient, parents, and clinicians were blinded. The placebo (Maalox and tonic water) resembled antibiotic in color, texture, and taste.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Follow up occurred at 2-3 days, 10-14 days, and 90 days. 12 patients (7%) were lost to follow-up (placebo group: 8 , antibiotic group: 4). 10-day follow-up: 60% in person, 40% by telephone. 90-day follow-up: 65%
Were patients analyzed in the groups to which they were randomized?	Use of Intention to treat analysis was not specifically stated though all patients who were randomized to a treatment group and not lost to follow were included in the primary analysis. Seven patients with treatment failure had antibiotics added or changed.
Was the trial stopped early?	No. The sample size determination required 162 patients yet only 149 were included in the primary analysis due to the 12 patients that were lost to follow up.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Demographic Data
N = 161, 12 lost to follow up
N = 149 (Placebo: 76, Antibiotics: 73)
Age (Median/IQR): 4 years (1-12 years)
41% prior abscess
47% family history of abscess
55.8% in the diaper area
Sedation: 69%
Wound packing 72%
Compliance: 66%
CA-MRSA: 80%,
Resistance: Clindamycin (18%), TMP/SMX (0%)

Primary Outcome: Failure Rate
Absolute Risk: Placebo Group: 4/76 = 5.3%
Absolute Risk: Antibiotic Group: 3/73 = 4.1%
Absolute Risk Difference: 1.2%, 95% CI (-∞ to 6.8%)
The upper limit of the CI does not exceed the equivalence threshold of 7% and therefore non-inferiority is supported.

Subgroup Analysis: Patients < 14 years
Absolute Risk: Placebo Group: 2/58 = 3.4%
Absolute Risk: Antibiotic Group: 1/62 = 1.6%
Absolute Risk Difference: 1.84%, 95% CI (-∞ to 6.5%)

Secondary Outcome: New lesions at 10 days
Absolute Risk: Placebo Group: 19/76 = 26.4%
Absolute Risk: Antibiotics Group: 9/73 = 12.9%
Absolute Risk Difference: 13.5%, 95% (CI -∞ to 24.3%)
Non-inferiority is not supported. The upper limit of the confidence interval exceeds 7%)

Secondary Outcome: New lesions at 90 days
No difference in new lesions at 90 days

Adverse Events: No difference, 90% without, most common: diarrhea (both) and rash (antibiotic group)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See confidence intervals above

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Age is similar to our population. We generally have patients come back at 2 day intervals for wound checks, and don't have them unpacking their own wounds. The study population had a very high rate of previous abscess (41%), family history of abscess (47%) and non-compliance despite being provided with the study medications (34%).
Were all patient important outcomes considered?	Yes. The discussion states that there was no correlation between treatment failure and other factors such as medical history, family history, use of would packing, the use of procedural sedation, clinical assessment of abscess size, erythema, induration, or the presence of cellulitis. This data was not presented Despite a high rate of prior abscess, the authors did not assess the colonization rate, clearance of colonization, or provide methods for decontamination which may be relevant for development of new lesions.
Are the likely treatment benefits worth the potential harm and costs?	The study suggests that antibiotic use prevented development of new lesions at 10-days. This is despite a 66% rate of compliance. However, there was no difference at 90 days. The risks of antibiotics include: antibiotic resistance, adverse events (e.g. Stevens-Johnson syndrome) and cost.

CLINICAL BOTTOM LINE

BACKGROUND: Several studies have demonstrated that incision and drainage of an abscess can be curative without antibiotics. Over the past several years, the incidence of skin abscesses has increased and there has been an emergence of Community Acquired Methicillin Resistant Staph Aureus (CA-MRSA). While incision and drainage had been standard of care without antibiotics, many are now prescribing antibiotics for MRSA suspicious lesions. The benefit of antibiotics for the treatment of the MRSA abscesses has not been established.

CLINICAL QUESTION: In children from 3 months to 18 years of age who undergo incision and drainage of a cutaneous abscess, is treatment without antibiotics non inferior to treatment with antibiotics in reducing treatment failures?

DESIGN/VALIDITY: This was a double blind, randomized, non-inferiority trial, of patients ages 3 months to 18 years undergoing incision and drainage of a simple cutaneous abscess. The primary outcome was treatment failure after incision and drainage of an abscess comparing Trimethoprim/Sulfamethoxazole and Placebo. Secondary outcomes were the development of new lesions at 10-day follow up and 90-day follow-up. The study included 149 patients with 76 in the Placebo group and 73 in the Antibiotic group. This was a population at high risk for treatment failures with a 41% history of a prior abscess and a 47% history of a family member with a prior abscess. Despite this there was no attempt to document colonization or colonization clearance and no de-colonization methods prescribed on discharge. The low rate of antibiotic compliance (66%) may result in underestimation of antibiotic efficacy though non-compliance is a pragmatic concern. A per protocol analysis may have been helpful to assess the impact of noncompliance.

PRIMARY RESULTS: 94.3% of the study population did not have a treatment failure. Placebo was non-inferior to antibiotics in the rate of treatment failure (Placebo Group: 5.3%, Antibiotic Group: 3/73 = 4.1%, Absolute Risk Difference = 1.2%, 95% CI (-∞, 6.8%). This was true despite medical history or family history, use of would packing, the use of procedural sedation for the incision and drainage, clinical assessment of abscess size, erythema, or induration, or the presence of cellulitis (data not presented). Placebo was <u>not</u> non-inferior to antibiotics for the development of new lesion at 10 days (Placebo Group: 26.4%, Antibiotics Group: 12.9%, Absolute Risk Difference: 13.5%, 95% CI (-∞ to 24.3%). However, the was no difference in the rate of development of new lesions at 90 days. There were no serious adverse events reported though the small sample size makes it unlikely to determine rare severe adverse events such as Stevens-Johnson syndrome with Trimethoprim-Sulfamethoxazole.

APPLICABILITY: The study population had a very rate of prior abscess (41%) and non-compliance with treatment (66%). This may decrease the apparent efficacy of antibiotics. Larger studies are required before the study's results may be generalizable to other populations.

AUTHOR'S CONCLUSION: "After incision and draining of skin abscesses in children, 95% of the skin abscesses demonstrated clinical resolution; therefore, antibiotics are not required. The potential benefit of preventing distal lesion development with the use of antibiotics will require further study and evaluation.

By avoiding unnecessary antibiotic use, potential adverse effects, allergic reactions, and natural selection of more resistant organisms may be avoided. Furthermore, the cost saving of unnecessary antibiotic use is significant, considering the dramatic increase in skin abscess diagnoses."

POTENTIAL IMPACT: This pilot study suggests that Placebo after abscess incision and drainage is non-inferior to Trimethoprim/Sulfamethoxazole. The small sample size, high risk population and high rate of non-compliance would suggest that a change in management strategy is not warranted until the results can be reproduced in a larger study.

ABSCESS INCISION & DRAINAGE: ANTIBIOTICS (META-ANALYSIS)

In children and adults with a cutaneous abscess, does the administration of antibiotics with MRSA coverage after abscess incision and drainage when compared to placebo result in a reduction in treatment failures on re-assessment?

Guillermo, De Angulo, MD, Michael Mojica, MD
February, 2019

Gottlieb M, DeMott JM, Hallock M, Peksa GD.

SYSTEMIC ANTIBIOTICS FOR THE TREATMENT OF SKIN AND SOFT TISSUE ABSCESSES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Ann Emerg Med. 2019 Jan;73(1):8-16
PubMed ID: 29530658

STUDY DEFINITIONS	
POPULATION	Inclusion: Randomized, controlled trials comparing systemic antibiotics with MRSA activity in the treatment abscesses after incision and drainage Exclusion: Case reports, case series, retrospective studies, non-randomized prospective studies, studies published in abstract form only
INTERVENTION	Systemic antibiotics with MRSA activity N = 3: Trimethoprim-Sulfamethoxazole N = 1: Trimethoprim-Sulfamethoxazole or Clindamycin
CONTROL	Placebo
CO-INTREVENTIONS	Abscess incision and drainage 2 studies utilized ultrasound for identification and management
OUTCOME	Primary Outcome: Treatment failure. As defined by the original study. Must include a specific assessment of the wound within 21 days 1 study: Clinical criteria only 3 studies: Clinical criteria and need for intervention (repeat I&D, admission, change in antibiotics) Secondary Outcomes: Recurrence rate for new abscesses Overall adverse event rates Rates of diarrhea
DESIGN	Systematic Review and Meta-analysis of Randomized Clinical Trials

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review explicitly address a sensible clinical question?	Yes. The question was explicit. However, the studies differed in the age of the population, the inclusion and exclusion criteria, the intervention and the criteria for treatment failure.
Was the search for relevant studies detailed and exhaustive?	The search included PubMed, SCOPUS, CINAHL, and the Cochrane data or systematic reviews and clinical trials registry (Inception to 2017). Bibliographies of identified studies were reviewed and topic experts were contacted. The search was not limited by language. The search strategy is included in the supplementary materials. Egger's test and a funnel plot (Figure 3) were used to assess publication bias. Evidence of publication was not present.
Was the risk of bias of the primary studies assessed?	Yes. Study quality was assessed using the Cochrane risk of bias tool (Table 2). All 4 studies were of low risk of bias. The article by Duong) had an unclear risk of bias for blinding of outcome assessment. No study was sponsored by pharmaceutical companies.
Were the selection and assessment of studies reproducible?	Two investigators assessed studies for inclusion and quality. Approval by both was required. Discrepancies were resolved by consensus. Inter-rater reliability was not assessed for inclusion or quality.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

Yes. I^2 = 0% for the primary outcome of treatment failure (odds ratio) but I^2 = 55% for the risk difference. The chi squared for the two measure of the study outcome were not statistically significant (indicating no heterogeneity). A random effects model (the more conservative statistical approach was utilized if heterogeneity existed.

WHAT ARE THE OVERALL RESULTS OF THE REVIEW?

N = 4 studies with 2,406 patients at 16 clinical sites, ED (3), ED and Outpatient (1)
Bacteriology: MRSA (49%), MSSA (16.3%)

	Treatment Failure		
	Yes	No	
Antibiotics	89	1066	1,155
Placebo	150	781	931

Antibiotic group: 7.7% (89/1,155)
Placebo group: 16.1% (150/931)
Risk Difference: Placebo – Antibiotics = 7.4%, 95% CI (2.8, 12.1%)
Relative Risk: Antibiotics/Placebo = 0.48, 95% CI (0.37, 0.61)

PRIMARY AND SECONDARY OUTCOMES

	Placebo	ABx	Risk Difference (95% CI)	Odds Ratio (95% CI)
Treatment Failure (Fig2)	16.1%	7.7%	7.4% (2.8, 12.1%)	2.32 (1.75, 3.08)
New Distal Lesions (Fig4)	15.3%	6.2%	-10.0% (-12.8, -7.2%)	0.32 (0.23, 0.44)
Adverse Events (Fig5)	22.2%	24.8%	4.4% (1.0, 7.8%)	1.29 (1.06, 1.58)
Rates of Diarrhea (Fig6)	11.2%	11.8%	0.8% (-1.7, 3.4%)	1.09 (0.84, 1.41)
GREEN = Statistically Significant, RED = Not Statistically Significant				

Adverse events: Majority were mild: GI, rash, headache, drowsiness

DID THE REVIEW ADDRESS CONFIDENCE IN EFFECT ESTIMATES?

Confidence intervals for the risk differences and odds ratios for the primary and secondary outcomes are presented in the table above. Because of the rarity of events, the confidence intervals are fairly wide.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were all patient-important outcomes considered?	Yes, they considered clinical cure rates, treatment failures, rate of new abscess formation, adverse events. These are the most important outcomes in regards to this disease process. Patients may also consider time lost from work or school and transmission of infection to household contacts as important outcomes
Are any postulated subgroup effects credible?	No. No subgroup effects were postulated.
What is the overall quality of the evidence?	The 4 included studies were assessed by the Cochrane risk of bias tool as low risk of bias. While the studies were of high quality, there were significant differences in the populations, interventions and outcome definitions that may preclude combining their results.
Are the benefits worth the costs and potential risks?	Potential risks associated with antibiotics including both minor (GI symptoms) and severe (Steven's Johnson syndrome) adverse events. Financial costs and the development of bacterial resistance should also be considered. There was a 4.4% increase in mild adverse events in the study. In addition, an increase in the use of antibiotics may increase bacterial resistance. The number needed to treat for the primary outcome was 14 (NNT = 1/ARD = 1/0.74 = 14). For every 14 patients treated with antibiotics after incision and drainage, 1 additional patient would not have a treatment failure. The number need to treat to prevent a new distal abscess was 10 (1/0.10). The number need to harm for mild adverse events was 23 (1/0.044).

CLINICAL BOTTOM LINE

BACKGROUND: The primary intervention for cutaneous abscesses has been incision and drainage. Traditionally, antibiotics are not administered unless a surrounding cellulitis is present. Recent evidence appears to contradict that approach. Two large, well-designed clinical trials including both adult and pediatric patients have demonstrated a benefit of antibiotics after abscess incision and drainage (Daum, NEJM. 2017, PubMed ID: 28657870, Talan, NEJM 2016, PubMed ID: 26962903). The 2016 study was criticized for including patients who would have otherwise had an indication for antibiotics. However, a planned subgroup analysis in patients with and without guideline recommended antibiotics also demonstrated improved outcomes in the antibiotics group (Talan, Annals EM 2018, PubMed ID: 28987525).

CLINICAL QUESTION: In children and adults with a cutaneous abscess, does the administration of antibiotics with MRSA coverage after abscess incision and drainage when compared to Placebo result in a reduction in treatment failures on re-assessment?

DESIGN/RISK OF BIAS: This was a meta-analysis of randomized controlled trials comparing the efficacy of antibiotics with staphylococcal (MRSA and MSSA) activity to placebo. The primary outcome was treatment failure. In 3 studies this was defined by clinical signs and symptoms and the requirement of an intervention and in 1 study by clinical signs and symptoms alone. The authors conducted an extensive search and found no evidence of publication bias. There were significant differences in the study methodologies. These included differences in inclusion, and exclusion criteria, the definition of treatment failure and timing of follow up assessments, antibiotics used and standardization of the abscess and drainage procedure. The studies were of high quality as assessed by the Cochrane risk of bias tool. However, there was no assessment of inter-rater reliability for study inclusion and quality.

PRIMARY RESULTS: The search yielded 4 clinical trials with 2,406 patients at 16 clinical sites. This included by pediatric and adult patients. The use of antibiotics after incision and drainage resulted in a decrease in treatment failures by 7.4%, 95% CI (2.8, 12.1%). In addition, there were fewer new lesions at other sites in those receiving antibiotics (-10.0%, 95% CI (-12.8, -7.2%)). There was however, a small but statistically significant increase in adverse events in the antibiotic group (4.4%. 95% CI (1.0, 7.8%)). The majority of adverse events were mild consisting of gastrointestinal symptoms, rash, headache and drowsiness. One patient developed fever, rash thrombocytopenia and hepatitis while on Trimethoprim-Sulfamethoxazole that resolved without sequelae.

PRIMARY AND SECONDARY OUTCOMES				
	Placebo	ABx	Risk Difference (95% CI)	Odds Ratio (95% CI)
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Rates of Diarrhea (Fig6)	11.2%	11.8%	0.8% (-1.7, 3.4%)	1.09 (0.84, 1.41)
GREEN = Statistically Significant, RED = Not Statistically Significant				

The number needed to treat for the primary outcome was 14 (NNT = 1/ARD = 1/0.074 = 14). For every 14 patients treated with antibiotics after incision and drainage, 1 additional patient would not have a treatment failure. The number need to treat to prevent a new distal abscess was 10 (1/0.10). The number need to harm for mild adverse events was 23 (1/0.044).

APPLICABILITY: The meta-analysis included 4 studies conducted at 16 clinical sites in both children and adults likely making it's result generalizable to those meeting the inclusion and exclusion criteria.

AUTHOR'S CONCLUSION: "The use of systemic antibiotics for skin and soft tissue abscesses after incision and drainage resulted in an increased rate of clinical cure. Providers should consider the use of antibiotics while balancing the risk of adverse events."

POTENTIAL IMPACT: The use of antibiotics with MRSA coverage after abscess incision and drainage reduced the proportion of patients with treatment failures and those developing abscesses at other sites at the cost of a small increase in mild adverse events. However, the possible risks with increase antibiotic use need to be considered. These include significant side effects like clostridium difficile infections, allergic reactions and Stevens-Johnson syndrome and increasing antibiotic resistance. Providers need to balance the risk and benefits when deciding to use adjuvant antibiotics.

ABSCESS INCISION & DRAINAGE: LOOP DISSECTION TECHNIQUE

In pediatric and adult patient with a cutaneous abscess does the loop drainage technique for incision and drainage (2 small pole incisions, blunt dissection and a vessel loop passed through both incisions and tied on the skin) when compared to convention incision and drainage (single incision, blunt dissection and packing) result in fewer treatment failures defined as the need for: repeat incision and drainage, antibiotics, hospital admission or operative intervention?

Nisha Narayana, MD, Joshua Beiner, MD
June 2018

Gottlieb M, Peksa GD.

COMPARISON OF THE LOOP TECHNIQUE WITH INCISION AND DRAINAGE FOR SOFT TISSUE ABSCESSES: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Am J Emerg Med. 2017 Jan;36(1):128-133.
PubMed ID: 28917436

STUDY DEFINITIONS	
POPULATION	Inclusion: Studies comparing LDT and CID with an outcome of treatment failure. All studies were performed either in the ED or in the ED and OR. Study design: Prospective or retrospective cohort or randomized clinical trial. No language or age restrictions Exclusion: Case series, case reports and abstracts only
INTERVENTION	Loop Drainage Technique (LDT): 2 small pole incisions, blunt dissection to break down loculations and a vessel loop passed through both incisions and tied loosely on the skin
CONTROL	Convention Incision and Drainage (CID): A single incision, blunt dissection to break down loculations and packing
CO-INTERVENTIONS	95% of the pediatric subgroup received empiric antibiotics compared to 54% in the adult subgroup. Indications for antibiotics were not presented.
OUTCOME	Primary Outcome: Treatment Failure As defined by individual studies and could include the need for: 1. Repeat incision and drainage (Trial 1, 2, 3 ,4) 2. Antibiotics (Trial 2: Ladde 2015) 3. Admission (Trial 2: Ladde 2015) 4. Operative Intervention (Trial 2: Ladde 2015) Study authors were contacted to delineate if more than one outcome occurred
DESIGN	Systematic Review and Meta-analysis of prospective, retrospective and randomized trials: Non-inferiority Hypothesis

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review explicitly address a sensible clinical question?	Yes. Initial studies have suggested that LDT is less painful, associated with better overall patient satisfaction and can reduce utilization of antibiotics and healthcare costs compared to CID. If found to be non-inferior to CID, these might be additional benefits conferred to the LDT. The intervention was clearly defined. However, the primary outcome of treatment failure was defined by the individual studies and was a composite outcome. The components of treatment failure are not of equivalent import. It did not explicitly state the patient population but pediatric and adult patients were later analyzed separately in sub-group analysis. The authors followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines.
Was the search for relevant studies detailed and exhaustive?	Yes. The search was conducted with a research librarian and included a number of databases (PubMed, CINAHL, SCOPUS, Cochrane database of systematic review and Cochrane clinical trials registry). Details of the search strategy were included in the paper, allowing for search reproducibility. In addition, the authors searched bibliographies of the identified studies and review articles and contacted topic experts. There were no language restrictions. Two investigators independently assessed studies for eligibility based on inclusion criteria. All abstracts meeting initial criteria were reviewed as full manuscripts. Studies determined to meet eligibility criteria on full text review by both extractors were included in final data analysis. Any discrepancies were resolved by consensus. A funnel plot (Figure 3) and Egger's test did not reveal evidence off publication bias though only 3 studies were included on the funnel plot and the p value for Egger's test was not presented.
Was the risk of bias of the primary studies assessed?	Yes. Quality was assessed by two reviewers using the Cochrane risk of bias tool for randomized trials and the modified Cochrane risk of bias tool for retrospective and prospective studies. Retrospective studies (n=3) are described as "low-moderate" risk of bias (Tables 2). The single randomized clinical trial is described as "fair" quality (Table 3).
Were the selection and assessment of studies reproducible?	Yes. Two investigators assessed each study for both inclusion and quality. Discrepancies were resolved by consensus. Inter-rater reliability for inclusion and quality were not presented.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

For treatment failure the Chi squared p = 0.66, I^2 = 0 and Forrest Plot (figure 2) indicate no heterogeneity. The random effects model was used (more conservative than fixed effects method)

WHAT ARE THE OVERALL RESULTS OF THE REVIEW?

N = 4 studies (460 patients)
Study design: RCT (1), retrospective cohort (3)
Population: Pediatrics (2): 78.5%, mean age 5 years, Adults (2): 21.5%, mean age 37.2 years

Primary Outcome: Treatment Failure (Figure 3)

	TREATMENT FAILURE		
	YES	NO	
Loop Drainage Technique (LDT)	8	187	195
Conventional Incision and Drainage (CID)	25	240	265

Absolute Risk (LDT): 8/195 = 4.1%
Absolute Risk (CID): 25/265 = 9.43%
Absolute Risk Difference (CID – LDT): 9.43% - 4.1% = 5.3%, 95% CI (0.5, 9.9%)
Relative Risk (CID/LDT): ((25/265)/(8/195)) = 9.43/4.1 = 2.3, 95% CI (1.1, 5.0)
Odds Ratio (CID/LDT): ((25/240)/(8/187)) = 2.63, 95% CI (1.0, 6.6) (presented by authors)
The authors describe the analysis as non-inferiority though a non-inferiority margin was not presented.

Subgroup Analysis: Age (Figure 4 and 5)
< 18 years: CID (16/225 = 7.1%), LDT (2/136 = 1.5%), OR 4.09, 95% CI (1.04, 16.12)
≥ 18 years: CID (9/40 = 22.5%), LDT (6/59 = 10.2%), OR 1.82, 95% CI (0.52, 6.37)

DID THE REVIEW ADDRESS CONFIDENCE IN EFFECT ESTIMATES?

Confidence intervals are presented for the risk difference and odd's ratios above. The 4 included studies were assessed as of low to moderate risk of bias. Observational studies (3 of the 4 included trials) had an inherently high risk of bias. The use of a composite primary outcome that was defined by each study raises concern particularly when the results based on each component of the composite outcome are not presented.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were all patient-important outcomes considered?	No. The only outcome presented was treatment failure. Other potential outcomes could include the pain of the procedure, revisits required and long term cosmetic outcomes.
Are any postulated subgroup effects credible?	Unclear. There was a statistically significant decrease in treatment failure in the LDT for the pediatric subgroup but not in the adult subgroup. There was no postulated reason for this difference. Treatment failure were more common in both adult treatment groups compared to the both pediatric treatment groups. Potential explanations for age subgroup effect were not presented. 95% of the pediatric subgroup received empiric antibiotics compared to 54% in the adult subgroup. Location and size of abscesses and presence of cellulitis are important confounding variables that were not presented.
What is the overall quality of the evidence?	The review states that studies were at an overall low to moderate risk of bias. Among the retrospective studies, one study was at moderate risk of possible confounding due to differences in age groups between patients, while the remainder was deemed low risk. Two studies were at moderate risk for departure from intended interventions, though both would have been biased in favor of improved outcomes in the CID. Two studies had moderate bias for missing data due to loss of patients to follow up. Finally, all three studies had moderate risk of biases for measurement of outcomes due to unclear blinding of the data abstractors. Studies were otherwise at low risk for bias. For the RCT, it was overall fair quality with low risk of bias in all categories except for unclear bias in the allocation concealment and blinding of outcome assessor categories. The quality of evidence may have been improved if there were more randomized controlled trials (vs. retrospective studies) included and if there was a larger number of total patients included in the data.
Are the benefits worth the costs and potential risks?	Overall, there was a statistically significant decrease in treatment failures in the LDT group. The number need to treat is 18.9 (NNT = 1/ARD = 1/0.053 = 18.9). For every 18.9 patients treated with LDT, 1 additional patient would avoid a treatment failure compared to CID. Other potential benefits include a reduction in pain during the procedure, the number of revisits required and long term cosmetic outcomes though these were not presented.

CLINICAL BOTTOM LINE

BACKGROUND: Conventional abscess incision and drainage includes a relatively large single mid-abscess incision followed by blunt dissection of the abscess cavity to break up loculations and wound packing. It is often difficulty to adequately anesthetize the area and patients describe the procedure as very painful. In addition, return visits for abscess repacking are often required and repeat incision and drainage may be required if the packing falls out. Finally, the procedure may leave a long scar. The loop dissection technique potentially avoids many of these complications. The technique involves making two small incisions at each pole of the abscess followed by blunt dissection to remove loculations. A vessel loop is then passed through each incision site and is tied loosely on the skin surface.

CLINICAL QUESTION: In pediatric and adult patient with a cutaneous abscess does the loop drainage technique for incision and drainage (2 small pole incisions, blunt dissection and a vessel loop passed through both incisions and tied on the skin) when compared to convention incision and drainage (single incision, blunt dissection and packing) result in fewer treatment failures defined as the need for: repeat incision and drainage, antibiotics, hospital admission or operative intervention?

DESIGN/RISK OF BIAS: This was a systematic review and meta-analysis of studies comparing conventional incision and drainage of a cutaneous abscess with the loop drainage technique. An exhaustive search strategy revealed only 4 studies meeting inclusion and exclusion criteria. 3 of the 4 trials included in the analysis were retrospective studies described as “low-moderate” risk of bias (Tables 2 and 3) by the modified Cochrane risk of bias tool. The single randomized clinical trial is described as “fair” quality by the Cochrane risk of bias tool. Inter-rater reliability for study inclusion and quality were not presented. It is rare to find a meta-analysis that includes a summary statistic based on studies of different designs (observational and interventional).

The study included a single composite outcome of treatment failure which was based on each study’s definition. A breakdown of results by each element of the composite outcome was not included. Study authors were contacted and specific study data was obtained to separate the combination of outcomes. Other potential outcomes including: the pain of the procedure, revisits required and long term cosmetic outcomes were not presented. 95% of the pediatric subgroup received empiric antibiotics compared to 54% in the adult subgroup. The authors describe the analysis as a non-inferiority though a non-inferiority margin was not presented.

PRIMARY RESULTS: 4 studies (460 patients) were included in the primary analysis. 4.1% (8/195) of patients in the LDT group and 9.43% if the CID group had a treatment failure. There was statistically a significant decrease in treatment failure in the LDT group compared to the CID group (Absolute Risk Difference: 5.3%, 95% CI (0.5, 9.9%), Relative Risk (CID/LDT): 2.3, 95% CI (1.1, 5.0). In the pediatric subgroup, there was a statistically significant decreased in treatment failure (Odds Ratio (CID/LDT): 4.09, 95% CI (1.04, 16.12)). There was not a statistically significant difference in treatment failures in the adult subgroup (Odds Ratio (CID/LDT) 1.82, 95% CI (0.52, 6.37). The reason for the difference in treatment failures in the subgroups is unclear though 95% of the pediatric subgroup received empiric antibiotics compared to 54% in the adult subgroup. A subgroup analysis based on antibiotic use would have been helpful

APPLICABILITY: The study's results are likely generalizable to pediatric patients with a cutaneous abscess receiving empiric antibiotics. The youngest infants are often drained by Pediatric surgery consults in the OR setting, and it might be helpful to know if there the indications for operative incision and drainage. Patients/parents are required to slide the loop back and forth on a daily basis to promote drainage and limit adhesions. The can also remove the loop themselves. It is unclear what proportion of our population would be comfortable with this approach. Larges abscess may require more than one loop. The need for a second loop may increase the pain of the procedure.

AUTHOR'S CONCLUSION: "The existing literature suggests that the Loop Dissection Technique is associated with a lower failure rate than Conventional Incision and Drainage. However, the data is limited by small sample sizes and predominantly retrospective study designs. Given the potential for less pain, decreased scarring, and lower associated healthcare costs, this technique may be considered for the treatment of skin and soft tissue abscesses in the ED setting, but further studies are needed."

POTENTIAL IMPACT: This meta-analysis suggests that the loop dissection technique may decrease treatment failures when compared to conventional incision and drainage. The potential for less procedural pain, a reduction in repeat visits and better cosmetic outcomes makes this technique an attractive alternative to conventional incision and drainage. Larger, high quality, randomized trials that include all relevant outcomes are needed to better delineate the risks and benefits of the loop dissection technique.

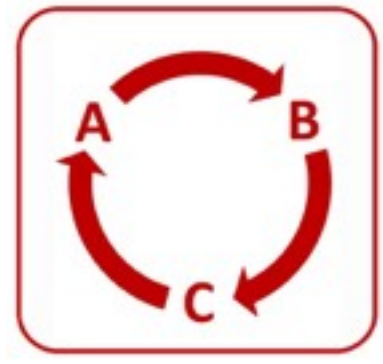
APPENDIX: PEDIATRIC STUDIES INCLUDED

McNamara WF, Hartin CW Jr, Escobar MA, Yamout SZ, Lau ST, Lee YH.
An Alternative to Open Incision and Drainage for Community-Acquired Soft Tissue Abscesses in Children.
J Pediatr Surg. 2010 Jun;45(6):1294-8., PubMed ID: 21376200

Ladde JG, Baker S, Rodgers CN, Papa L.
The LOOP Technique: A Novel Incision and Drainage Technique in the Treatment of Skin Abscesses in a Pediatric ED.
Am J Emerg Med. 2015 Feb;33(2):271-6., PubMed ID: 25435407

PROCEDURE: LOOP DISSECTION TECHNIQUE
Two small incisions (4-5 mm) are spaced 4-5 cm apart within the abscess cavity at the abscess poles (Abscesses larger than 4-5 cm may require more than 1 loop)
Blunt dissection of the abscess cavity to break up loculations
A sterile vessel loop, Penrose drain or rubber band is threaded in one excision and exits to the skin from the 2nd incision
The loop is tied together to form a loose loop, preventing it from falling out.
The patient is encouraged to slide the loop back and forth on a daily basis to facilitate drainage and prevent adhesions.
The drain can be cut and removed at home when it stops draining and cellulitis (if present initially) resolves (typically after 7 days).
VIDEO LINK: ALIEM LOOP DRAINAGE TECHNIQUE

ENDOCRINE & METABOLIC



1. DKA: Cerebral Edema Risk Factors: NEJM. 2001
2. DKA: Fluid Rate and Tonicity: NEJM 2018
3. Fluids: Saline vs Balanced Crystalloid: NEJM 2018
4. Hyponatremia: ICU Fluids: Pediatr Crit Care Med. 2008
5. Hyponatremia: Maintenance Fluids: Pediatrics 2004

DIABETIC KETOACIDOSIS: CEREBRAL EDEMA RISK FACTORS

In pediatric patients with diabetic ketoacidosis are demographic characteristics, initial biochemical characteristics, therapeutic interventions, or changes in biochemical values during treatment associated with an increased risk of cerebral edema?

Michael Mojica, M.D.
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Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, Kaufman F, Quayle K, Roback M, Malley R, Kuppermann N; Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics.

RISK FACTORS FOR CEREBRAL EDEMA IN CHILDREN WITH DIABETIC KETOACIDOSIS.

N Engl J Med. 2001 Jan 25;344(4):264-9.,
PubMed ID: 11172153

STUDY DEFINITIONS	
CASES	Inclusion: < 18 years with cerebral edema related to diabetic ketoacidosis Diabetic Ketoacidosis: Glucose > 300 mg/dl, venous pH < 7.25 OR serum bicarbonate <15 mmol/liter, (+) ketones in the urine Cerebral Edema: 1. Altered mental status: Obtunded or disoriented AND 2a. Radiographically or pathologically confirmed cerebral edema. Patients with infarction, consistent with cerebral edema were included OR 2b. Specific treatment for cerebral edema: Hyperosmolar therapy or controlled hyperventilation followed by clinical improvement. Exclusion: None specified Setting: 10 Pediatric Centers, 1982-1997
CONTROLS	Random Controls: Randomly selected from a computer-generated list of children admitted for diabetic ketoacidosis at each center during the study period. 3 Random controls were selected for case Matched Controls: Children with diabetic ketoacidosis were matched to children with cerebral edema based on: 1. Age (within two years) 2. On-set of diabetes (established vs. newly diagnosed disease) 3. Venous pH at presentation (within 0.1). If pH not available, matched according to serum bicarbonate 4. Serum glucose concentration at presentation within 200 mg/dl 5. Matched controls were selected for case. If > 3 match controls were identified those whose admission date were closest were chosen. Exclusion: None specified Setting: 10 Pediatric Centers, 1982-1997
OUTCOME	Association of risk factors with the development of cerebral edema
DESIGN	Observational: Case-Control Study

HOW SERIOUS WAS THE RISK OF BIAS (CASE-CONTROL)

DID THE CASES AND CONTROLS HAVE THE SAME RISK FOR BEING EXPOSED IN THE PAST?	
Were cases and controls similar with respect to the indication or circumstances that would lead to exposure? (or did statistical adjustments address the imbalance).	No. The patients with cerebral edema when compared to <u>random</u> controls were younger, white, and newly diagnosed diabetes. They had more severe acidosis, hypocapnia, higher serum glucose, urea nitrogen, and creatinine at presentation. Logistic regression was used to adjust statistically for potential confounders. Yes. The patients with cerebral edema when compared to <u>matched</u> controls were similar with respect to age, newly diagnosed diabetes, glucose and pH. Children with cerebral edema had significantly higher serum urea nitrogen and significantly lower partial pressures of arterial carbon dioxide. Conditional logistic regression was used to adjust statistically for potential confounders.
Were the circumstances and methods for determining exposure similar for cases and controls?	Yes. Records of children admitted for diabetic ketoacidosis that indicated that they had had cerebral edema, cerebral infarction, coma, seizures, or death, or that they had undergone computed tomographic scanning, magnetic resonance imaging, intubation, or treatment with mannitol. Control patients were identified from the same records.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

<u>Demographic Data</u>
Cerebral edema: 0.9% (61/6,977), 95% CI (0.7, 1.1%)
Cerebral edema confirmation: 52% imaging, 44% response to therapy, 4% autopsy
Onset: Median 7 hours, range 0-24 hours. In 3 cases (5%) cerebral edema occurred prior to onset of treatment
Outcomes: 57% survived without neurologic sequelae, 21% with permanent neurologic sequelae, 21% died.

<u>Random Controls: Independent Predictors of C Edema</u>
BUN: RR 1.7 (1.2, 2.5) per increase of 9 mg/dl

$PACO_2$: RR 3.4 (1.9, 6.3) per decrease of 7.8 mmHg

<u>Matched Controls: Independent Predictors of C Edema</u>
BUN: RR 1.8 (1.2–2.7) per increase of 9 mg/dl

$PACO_2$: RR 2.7 (1.4–5.1) per decrease of 7.8 mmHg
↑ Na: RR 0.6 (0.4, 0.9) per increase 5.8 mmol/L/hour
NaHCO3 Treatment: RR 4.2 (1.5, 12.1)

HOW PRECISE IS THE ESTIMATE OF THE RISK?

See confidence intervals for the relative risks above.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Unclear. Age, gender, the proportion of white race and proportion presenting for the initial diagnosis of diabetes are the only demographic characteristics presented. The proportion in DKA presenting with their initial diagnosis of diabetes was 39% in the random control group. This seems high. The inclusion of 10 centers likely makes the results generalizable. The study enrollment period was 15 years and it is unclear if changes in the management of DKA had occurred over that time period.
Was follow-up sufficiently long?	Patients records were reviewed until hospital discharge. The median onset to diagnosis of cerebral edema was 7 hours with a range of 7-24 hours. It is unlikely that cerebral edema occurred after discharge.
Is the exposure similar to what might occur in my patient?	The “exposure” is laboratory data at presentation (BUN and PCO_2). This is likely to occur in our population and particularly in those with new onset of diabetes. The only exposure that was an intervention is the use of $NaHCO_3$ which typically is no longer used in part because of the results of this study.
What is the magnitude of the risk?	The relative risk was greatest for treatment with NaHCO3 (RR 4.2, 95% CI (0.4, 3.0). This is the only dichotomous variable. The other significant predictors of cerebral edema were continuous variables and the relative risk cannot be directly compared because each is expressed as an increase or decrease with a range specific to the variable. Beta coefficients, which would have allowed for direct comparison were not presented.
Are there any benefits that offset the risks associated with exposure?	No. There is no potential benefits associated with being sicker on presentation of for therapy with bicarbonate.

CLINICAL BOTTOM LINE

BACKGROUND: Cerebral edema is the most serious complication of diabetic ketoacidosis accounting for many deaths in children with diabetes. One theory suggests that children with diabetic ketoacidosis may develop cerebral edema due to the accumulation of osmolytes in brain cells exposed to hyperosmolar conditions. A rapid decrease in extracellular osmolality could result in osmotically mediated brain swelling. If clinical or management factors can be associated with the development of cerebral edema than interventions may be targeted to prevent this complication.

CLINICAL QUESTION: In pediatric patients with diabetic ketoacidosis are demographic characteristics, initial biochemical characteristics, therapeutic interventions, or changes in biochemical values during treatment associated with an increased risk of cerebral edema?

DESIGN/RISK OF BIAS: This is a case-control study that included two control groups. The cases consisted of 61 pediatric patients with diabetic ketoacidosis and cerebral edema. The random control group without cerebral edema consisted of 181 randomly selected patients with diabetic ketoacidosis. The matched control group without cerebral edema consisted of 174 children matched to those in the cerebral-edema group for: age at presentation, onset of diabetes (established vs. newly diagnosed), initial serum glucose concentration, and initial venous pH.

This is a well-designed study but susceptible to biases inherent to a retrospective case control study. This was however the only feasible design. 61 cases (of cerebral edema were identified over a 15-year span in 10 hospitals (1 case/hospital/30 months). The incidence of cerebral edema in patients admitted with DKA was 0.9% (61/6,977) over the study period. The presence of cerebral edema was defined in 1 of 3 ways. In the presence of altered mental status. 1. Imaging consistent with cerebral edema (52%), 2. Clinical improvement after therapy aimed at reducing cerebral edema (hyperventilation or hyperosmolar therapy) (44%) and 3. Autopsy (4%). Thus, the diagnosed of cerebral edema was not confirmed by imaging or autopsy in 44% of patients.

PRIMARY RESULTS: Children with cerebral edema compared to random controls were more likely to be younger, white, and newly diagnosed diabetes. Those with cerebral edema were more likely to present with more severe acidosis and hypocapnia and had higher serum glucose, urea nitrogen, and creatinine.

In the logistic regression analysis comparing the cerebral edema cases with random controls both BUN (RR 1.7, 95% CI (1.2, 2.5) per increase of 9 mg/dl and P_aCO_2: RR 3.4, 95% CI (1.9, 6.3) per decrease of 7.8 mmHg were independent predictors of cerebral edema.

In the conditional logistic regression analysis comparing the cerebral edema cases with matched controls both BUN (Relative Risk: 1.8, 95% CI (1.2, 2.7) per increase of 9 mg/dl and P_aCO_2: Relative Risk: 2.7, 95% CI (1.4, 5.1) per decrease of 7.8 mmHg were again independent predictors of cerebral edema. In addition, a slower rate of increase in serum of sodium (Relative Risk: 0.6, 95% CI (0.4, 0.9) per increase 5.8 mmol/L/hour) and treatment with sodium bicarbonate was associated with an increased risk of cerebral edema (Relative Risk: 4.2, 95% CI (1.5, 12.1)).

APPLICABILITY: Age, gender, the proportion with white race and proportion presenting for the initial diagnosis of diabetes are the only demographic characteristics presented. The proportion with diabetic ketoacidosis presenting with their initial diagnosis of diabetes was 39% in the random control group. This seems high. The inclusion of 10 centers likely makes the results generalizable. The study enrollment period was 15 years and it is unclear if changes in the management of DKA could have occurred over that time period. The consistency of data recording was excellent, with a median kappa statistic of 0.9 (range, 0.6 to 1.0).

AUTHOR'S CONCLUSION: "We conclude that children with diabetic ketoacidosis who present with high initial serum urea nitrogen concentrations and low partial pressures of arterial carbon dioxide are at increased risk for cerebral edema. In addition, the lack of an increase in the serum sodium concentration during therapy is associated with an increased probability of cerebral edema. Children with these biochemical features should be monitored extensively for signs of neurologic deterioration, and hyperosmolar therapy should be available for immediate use in case early signs of cerebral edema occur. Finally, treatment with bicarbonate is associated with an increased risk of cerebral edema and should be avoided in most circumstances."

POTENTIAL IMPACT: The authors conclude their results do not fully support the osmotic gradient hypothesis of cerebral edema development in DKA as variables associated with rapid shifts in extracellular osmolality such as the change in serum glucose concentration and the rate of fluid administration) were not independent predictors of cerebral edema in either of the regression analyses. The authors instead suggest that cerebral ischemia may play a bigger role in the development of cerebral edema than previously thought as "both hypocapnia, which causes cerebral vasoconstriction, and extreme dehydration would be expected to decrease perfusion of the brain. In addition, bicarbonate therapy causes central nervous system hypoxia in laboratory animals with diabetic ketoacidosis."

Patients presenting with severe elevation or BUN or hypocapnia and those with a slow rise in serum sodium should be monitored closely for signs of cerebral. Confirmation of cerebral edema based on imaging should not delay therapy. In addition, the use of sodium bicarbonate should be avoided.

DIABETIC KETOACIDOSIS: FLUID RATE AND TONICITY

In pediatric patient with diabetic ketoacidosis is the rate and tonicity of intravenous fluid administration associated with an increased risk of poor in-hospital and long term neurocognitive outcomes?

Michael Mojica
June 2018

Kuppermann N, Ghetti S, Schunk JE, Stoner MJ, Rewers A, McManemy JK, Myers SR, Nigrovic LE, Garro A, Brown KM, Quayle KS, Trainor JL, Tzimenatos L, Bennett JE, DePiero AD, Kwok MY, Perry CS 3rd, Olsen CS, Casper TC, Dean JM, Glaser NS; PECARN DKA FLUID Study Group.

CLINICAL TRIAL OF FLUID INFUSION RATES FOR PEDIATRIC DIABETIC KETOACIDOSIS.

N Engl J Med. 2018 Jun 14;378(24):2275-2287.
PubMed ID: 29897851

STUDY DEFINITIONS	
POPULATION	Inclusion: < 18 years of age, diabetic ketoacidosis defined as: glucose > 300 mg/dl and either pH < 7.25 or HCO_3 < 15 mmol/liter Exclusion: 1. Comorbidities that could influence neurocognitive assessment 2. Concurrent alcohol or narcotic use 3. Head trauma or other conditions affecting neurologic function 4. Substantial treatment of DKA prior to enrollment (e.g. transferred patients) 5. Pregnancy 6. Conditions for which specific fluid or electrolyte therapy are indicated 7. GCS 11 (after 2nd year of enrollment) Setting: PECARN Network: 13 Urban Children's Hospital ED's, 2/2001-9/2016
INTERVENTION	1. Fast rate with 0.9% normal saline 2. Fast rate with 0.45% normal saline 3. Slow rate with 0.9% normal saline 4. Slow rate with 0.45% normal saline Fast: ½ fluid deficit replaced over 12 hours, remainder of deficit and maintenance fluids over subsequent 24 hours Slow: Fluid deficit replaced with maintenance fluids over 48 hours
CO-INTERVENTIONS	1. Fluid bolus of 10 ml/kg normal saline. Subtracted from fluid deficit. Could be repeated to restore perfusion or hemodynamic instability 2. Insulin infusion of 0.1 units/kg/hour 3. Glucose added to infusion to maintain glucose in the range of 100-200 mg/dl if serum glucose fell below 200-300 mg/dl 4. Potassium replacement: Equal mixture of potassium chloride and phosphate.
OUTCOME	Primary Outcome: Neurologic deterioration: 2 consecutive GCS < 14 during any hour within the first 24 hours (proportion of patients, magnitude and duration of decrease). GCS measured hourly for the 1st 24 hours or until DKA resolution (defined as the transition to subcutaneous insulin). Repeated in 15 minutes if < 14 (Note: Patients with initial QCS < 14 excluded from analysis of the primary outcome Secondary Outcomes: 1. Clinically Apparent Brain Injury: Deterioration in neurologic status leading to: hyperosmolar therapy, endotracheal intubation, or death (each case confirmed by a blinded adjudication committee). 2. Short-Term Memory: Patients > 3 years. Forward and backward digit span recall (range 0-16) with higher score indicating better memory). Repeat Q4 hours during waking hours for the 1st 24 hours or until DKA resolution (defined as the transition to subcutaneous insulin) 3. Long-Term Outcomes: Patients > 3 years, 2-6 months post discharge a. Short-Term Memory: Digit span recall (see above) b. Contextual Memory: Color, spatial tasks (simplified version for 3-5 years) c. IQ Testing: Wechsler Abbreviated Scale of Intelligence (≥ 6 years) Wechsler Preschool and Primary Scale of Intelligence short form (3-5 yrs) Prespecified subgroups: Age (< 6 years or ≥ 6 years), baseline GCS and prior history of DKA (yes/no).
DESIGN	Interventional: Randomized clinical trial: 2x2 Factorial design

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized to 1 of the 4 treatment regimens. Randomization was stratified by baseline GCS (≥ 14 or < 14) and treatment center.
Was randomization concealed?	Unclear. The details of the randomization process were not presented.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Demographic and clinical characteristics are listed in table 2. There were no clinically significant differences in the 4 treatment groups.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Yes. Patients, their parents/guardians and outcome assessor at the 2-6 month follow up were blinded to treatment group assignment. Each case of clinically apparent brain injury was confirmed by a blinded adjudication committee. Clinicians caring for the patient were not blinded.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. For the short term, in-hospital outcomes. No for the long-term outcomes. 387 (30.1%) of children older than 3 years were lost to follow up or declined follow up testing.
Were patients analyzed in the groups to which they were randomized?	Yes. The primary analysis was performed as an intention to treat analysis. Secondary analyses were also performed on the per protocol population (underwent randomization and received fluids as per protocol) and safety population (all patients that received any trial fluid).
Was the trial stopped early?	No. The sample size determination indicated that 1,360 episodes of DKA were needed for an effect size of a 7.5% difference in the primary outcome. 1,361 DKA episodes had an initial GCS of ≥ 14 and were included in the analysis of the primary outcome.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Demographic Data
N = 1,389 DKA episodes (1,119 patients with 1 episode, 132 x 2 episodes, 2 x 3 episodes)
Approximately 50% with new onset IDDM
Initial GCS: 15 (91%), 14 (7%), < 14 (2%),
N = 1,361(98%) DKA episodes with baseline GCS ≥ 14 (included in analysis of primary outcome)

Decrease in GCS to less than 14: 48 (3.5%)
Clinically apparent brain injury: 12 (0.9%), 11 of 12 recovered without overt neurologic injury, most of these patients had severe acidosis or hypocapnia
Death: 1 (0.07%), only patient intubated

ABSOLUTE RISK: IN-HOSPITAL NEUROLOGIC OUTCOMES

	FAST (0.45%)	FAST (0.9%)	SLOW (0.45%)	SLOW (0.9%)
%GCS → < 14	3.0% (10/337)	3.2% (11/345)	3.3% (11/338)	4.7% (16/341)
Clinical Brain Injury	0.6% (2/344)	0.6% (2/351)	1.4% (5/345)	0.9% (3/349)

The authors consider a 7.5% difference in the proportion with the primary outcome to be clinically significant in their sample size determination. With the highest rate of 4.7% it would not be possible to demonstrate an improvement of 7.5%.

RELATIVE RISK: IN-HOSPITAL NEUROLOGIC OUTCOMES

	FAST or 0.45%	SLOW or 0.9%	RR (95% CI)
%GCS → < 14 (Fast/Slow)	3.1% (21/682)	3.9% (27/679)	0.76 (0.44, 1.33)
%GCS → < 14 (0.45%NS/0.9%NS)	3.1% (21/675)	3.9% (27/686)	0.80 (0.46, 1.40)
Clinical Brain Injury (Fast/Slow)	0.06% (4/695)	1.1% (8/694)	0.49 (0.15, 1.64)
Clinical Brain Injury (0.45%NS/0.9%NS)	1.0% (7/689)	0.1% (5/700)	1.43 (0.46, 4.40)
GREEN = Statistically Significant, RED = Not Statistically Significant			

RELATIVE RISK: NEUROLOGIC DETERIORATION (SUBGROUPS)

Subgroups	RR (Fast/Slow), 95% CI	RR (0.45%/0.9%), 95%CI
All	0.76 (0.44, 1.33)	0.80 (0.46, 1.40)
Age < 6 years	0.62 (0.23, 1.63)	0.77 (0.30, 2.00)
Age 6-18 years	0.84 (0.43, 1.65)	0.76 (0.39, 1.50)
Previous DKA No	0.67 (0.35, 1.30)	0.62 (0.32, 1.19)
Previous DKA Yes	1.27 (0.41, 3.94)	1.54 (0.50, 4.79
GREEN = Statistically Significant, RED = Not Statistically Significant		

There was no statistically significant difference in the primary outcome (supplementary material):
1. The magnitude or duration of decreased in GCS
2. Digit recall performance in-hospital
3. Patients in the lowest quartile for pH or HCO3 or highest quartile for BUN or glucose
4. Subgroups by age or initial onset of IDDM (see table below)
5. Per protocol analysis: Excluded 7.9% of episodes for the primary outcome and 8.3% of episodes for the secondary outcomes who did not receive assigned study fluids.
6. Time to DKA resolution (approximately 14 hours) or hospital discharge (approximately 48 hours)

Non-Neurologic Adverse Events
There was a statistically significant increase in the proportion of episodes with hyperchloremic metabolic acidosis and hypocalcemia with fast compared to slow fluid administration
There was a statistically significant increase in the proportion of episodes with hyperchloremic metabolic acidosis. hypocalcemia and hypophosphatemia with 0.9% compared to 0.45%
No differences in hypoglycemia, hypokalemia
No difference in thrombosis (0), renal failure (0), pancreatitis (1), pulmonary edema (1) or cardiac arrhythmia (10).

Late Outcomes: Short term memory, contextual memory, IQ testing
No significant differences for neurocognitive outcomes in any of the study groups

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?
Despite the last sample size, the low rate of adverse outcomes resulted in wide confidence intervals around the presented relative risks

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. The study's results are likely generalizable to patient meeting the study's inclusion and exclusion criteria. The applicability to non-specialized Children's hospital settings is unclear.
Were all patient important outcomes considered?	Yes. There was a comprehensive list of adverse events. In addition, traditional outcomes such a time to resolution of DKA (14 hours) and time to discharge (48 hours) were included in the supplementary materials. Since the primary outcome was a decrease in the Glasgow Coma scale to less than 14 it would have been helpful to: 1. measure inter-rater reliability of this assessment particularly in younger children where the verbal component of the score may be more difficult to assess and 2. analyze the outcomes stratified by initial GCS of 14 or 15.
Are the likely treatment benefits worth the potential harm and costs?	The is a theoretic benefit of increased cerebral perfusion by more rapid rehydration though that benefit was not seen in this study. Hypochloremic metabolic acidosis and hypocalcemia were more common with rapid fluid replacement and 0.9% (normal) saline though the magnitude of the difference was not presented and the clinical significance of the difference are unclear.

CLINICAL BOTTOM LINE

BACKGROUND: The most concerning complication of diabetic ketoacidosis (DKA) and its treatment is cerebral edema. It is the primary cause of death in childhood DKA. The etiology of cerebral edema is unclear. One theory suggests that it may result from rapid osmotic shifts in the central nervous system. Recent evidence suggests that cerebral hypoperfusion/reperfusion and neuroinflammation may be causative. Guidelines recommend deficit replacement with isotonic fluids over 48 hours to prevent rapid shifts in osmolarity though the evidence to support this practice is limited to observation studies and consensus opinion (ISPAD, Pediatric Diabetes 2014, PubMed ID: 25041509).

In a well-designed, case-control study including 61 episodes of confirmed cerebral edema, (Glaser, NEJM 2001, PubMed ID: 11368049) the level of hypocapnia and degree of dehydration (as indicated by BUN measurement), and a slower rate of increase in serum sodium was associated with the development of cerebral edema. A bolus of sodium bicarbonate was the only treatment variable associated with the development of cerebral edema. From a therapy standpoint, the following were not independent predictors of cerebral edema: the rate of decrease in glucose or increase in HCO3, an initial insulin bolus or the infusion rate of fluids, sodium or insulin.

CLINICAL QUESTION: In pediatric patient with diabetic ketoacidosis is the rate and tonicity of intravenous fluid administration associated with an increased risk of poor in-hospital or long term neurocognitive outcomes?

DESIGN/VALIDITY: This was a well-designed, multicenter randomized clinical trial that took place in 13 Urban Children's Hospital emergency department in the PECARN Network from 2/2001 to 9/2016. Patients were randomized to 1 of 4 treatment groups based on the rate of deficit fluid administration and the tonicity of the fluids (0.9% NS versus 0.45% NS). Fast fluid administration was defined as one half of the fluid deficit replaced over 12 hours and the remainder of the deficit and maintenance fluids over subsequent 24 hours. Slow fluid administration was defined as the fluid deficit replaced with maintenance fluids over 48 hours.

Diabetic ketoacidosis was defined as a glucose greater than 300 mg/dl and either a pH less than 7.25 or HCO3 less than 15 mmol/liter. This definition does not included ketonemia or ketonuria and also differs from the ISPAD guideline's definition (Hyperglycemia >11mmol/L (200 mg/dl), Venous pH <7.3 or bicarbonate <15mmol/L and Ketonemia and ketonuria).

The primary outcome was the proportion, magnitude and duration of the decline of 2 consecutive GCS to less than 14 during any hour within the first 24 hours of enrollment. The secondary outcome of clinically apparent brain injury was defined as deterioration in neurologic status leading to: hyperosmolar therapy, endotracheal intubation, or death. One could argue that this is the more clinically relevant of the outcomes. This occurred in only 12 episodes (0.9%) and it may not be feasible to power a study looking for changes from the baseline rate.

PRIMARY RESULTS: 1,389 DKA episodes were included with 134 patients with more than 1 episode of DKA, Baseline GCS was 15 (91%), GCS 14 (7%), GCS less than 14 (2%). There were 1,361 DKA episodes with a baseline GCS of greater than or equal to 14 included in analysis of primary outcome. 48 (3.5%) of episodes had a decrease in GCS to less than 14. Clinically apparent brain injury occurred in 12 (0.9%) episodes. 11 of the 12 recovered without overt neurologic injury. The majority of these episodes were associated with severe acidosis or hypocapnia. One patient (0.07%) died.

There was no difference between the 4 study groups in the proportion or patients developing a GCS of less than 14 as well as the magnitude and duration of the decline in GCS. This was also true for the proportion with clinical apparent brain injury requiring treatment or resulting in death. There were no differences in either of these outcomes in the subgroups specified by age or prior history of DKA. The authors report a predefined subgroup analysis based on initial GCS but that data is not presented. It may have been helpful to analyze those with a GCS or 15 (91%) compared to 14 (7%).

There was no difference in the time to resolution of DKA (approximately 14 hours) and time to discharge (approximately 48 hours). It does not seem reasonable to plan for rehydration over 48 hours given these time frames.

ABSOLUTE RISK: IN-HOSPITAL NEUROLOGIC OUTCOMES				
	FAST 0.45%NS	FAST 0.9%NS	SLOW 0.45%NS	SLOW 0.9%NS
%GCS → < 14	3.0% (10/337)	3.2% (11/345)	3.3% (11/338)	4.7% (16/341)
Clinical Brain Injury	0.6% (2/344)	0.6% (2/351)	1.4% (5/345)	0.9% (3/349)

The authors considered a 7.5% difference in the proportion with the primary outcome to be clinically significant in their sample size determination. With the greatest difference between two groups of 1.7% it would not have been possible to reach the authors clinically significant difference.

RELATIVE RISK: IN-HOSPITAL NEUROLOGIC OUTCOMES			
	FAST or 0.45%	SLOW or 0.9%	RR (95% CI)
%GCS → < 14 (Fast/Slow)	3.1% (21/682)	3.9% (27/679)	0.76 (0.44, 1.33)
%GCS → < 14 (0.45%NS/0.9%NS)	3.1% (21/675)	3.9% (27/686)	0.80 (0.46, 1.40)
Clinical Brain Injury (Fast/Slow)	0.06% (4/695)	1.1% (8/694)	0.49 (0.15, 1.64)
Clinical Brain Injury (0.45%NS/0.9%NS)	1.0% (7/689)	0.1% (5/700)	1.43 (0.46, 4.40)
GREEN = Statistically Significant, RED = Not Statistically Significant			

There was no statistically significant is short term memory while in DKA. There were no statistically significant differences in short term memory, special memory or IQ testing at 2-6 months after discharge though 30.1% of children older than 3 years were lost to follow up or declined testing.

There was a statistically significant increase the proportion of episodes with hyperchloremic metabolic acidosis and hypocalcemia with FAST fluid administration and 0.9% normal saline. The clinical significance of these differences is unclear. There were no differences in hypoglycemia or hypokalemia and no difference in thrombosis (0), renal failure (0), pancreatitis (1), pulmonary edema (1) or cardiac arrhythmia (10) those there were rare.

APPLICABILITY: The study's results are likely generalizable to patient meeting the study's inclusion and exclusion criteria. The applicability to non-specialized Children's hospital settings is unclear. The DKA definition used in the study used a higher cutoff for glucose and lower cutoff for pH than that recommended by ISPAD guidelines so that the study population may be sicker than the general population of patients with DKA. The applicability of the study's results to patients with mild DKA is unclear thought it would have been more difficulty to find a difference in the neurocognitive outcomes in these lower risk patients.

Since the primary outcome was a decrease in the Glasgow Coma scale to less than 14 it would have been helpful to measure inter-rater reliability of this assessment particularly in younger children where the verbal component of the score may be more difficult to assess.

AUTHOR'S CONCLUSION: "In conclusion, in this prospective, randomized trial, neither the rate of administration nor the sodium chloride content of intravenous fluids significantly influenced neurologic outcomes of diabetic ketoacidosis in children."

POTENTIAL IMPACT: Guideline recommendations for the slow administration of isotonic fluids for pediatric patients with diabetic ketoacidosis are based primarily on limited observational data and expert consensus. There has been a shift away from the osmotic changes hypothesis of cerebral edema to a hypothesis of cerebral under perfusion and reperfusion with resulting neuro-inflammation.

This was a well-designed, multicenter randomized trial with 1,389 episodes of diabetic ketoacidosis requiring five and a half years of enrollment. There was no difference in any of the treatment groups in any of the study outcomes. Unfortunately, the study neither supports nor refutes current ISPAD recommendations primarily because it is underpowered to find a difference in the rare outcomes of decrease in GCS to less than 14 (n=48 (3.5%)) or clinical apparent brain injury requiring intervention or resulting in death (n=12, (0.9%)).

FLUIDS AND ELECTROLYTES: BALANCED ELECTROLYTES VS SALINE (ADULTS)

In adult patients who are admitted to a non-ICU setting and receive at least 500 ml of intravenous crystalloid in the Emergency Department, do Balanced electrolyte solutions (Ringer's Lactate or Plasmalyte A) when compared to Normal Saline result in a greater number of hospital free days within 28 days of admission and a lower incidence of a major adverse kidney events?

Michael Mojica, MD

January 2019

Self WH, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, Slovis CM, Lindsell CJ, Ehrenfeld JM, Siew ED, Shaw AD, Bernard GR, Rice TW;

BALANCED CRYSTALLOIDS VERSUS SALINE IN NON-CRITICALLY ILL ADULTS

N Engl J Med. 2018 Mar 1;378(9):819-828.
PubMed ID: 29485926

STUDY DEFINITIONS	
POPULATION	Inclusion: Adult (≥ 18 years), non-critically ill (admitted to a non-ICU setting), received > 500 ml crystalloid in the Emergency Department Exclusion: Admit to ICU, Balanced crystalloids were relatively contraindicated in the setting of hyperkalemia and brain injury. Use in these situations was at the treating clinician's discretion Setting: Single Center (US), 1/2016-4/2017
INTERVENTION	Normal Saline (see Appendix for composition)
CONTROL	Ringer's Lactate or Plasmalyte A (see Appendix for composition)
CO-INTERVENTIONS	The volume of fluid received in the ED and the volume and composition of fluids administered after admission were at the treating clinician's discretion
OUTCOME	Primary Outcome: Hospital free days until day 28 1. In-hospital death (all-cause mortality) OR 2. Number of days alive and out of the hospital between ED visit and 28 days a. = 0 days if died during stay or admitted for > 28 days b. = 28 – Length of Stay (days) if discharged before 28 days Secondary Outcomes: 1. Major adverse kidney events within 30 days. A composite of a. Death b. New renal replacement therapy before discharge or within 30 days c. Persistent renal dysfunction: Final serum creatine concentration > 200% of baseline at earliest of hospital discharge of within 30 days of admit 2. ≥ Stage II acute kidney injury (based on KDIGO creatinine criteria) a. ↑ Serum creatinine > 200% of baseline b. ↑ Serum creatinine to > 4 mg/dl with an absolute ↑ > 0.5 mg/dl c. New renal replacement therapy before discharge or within 30 days 3. Death before hospital discharge regardless of length of stay Note: Patients with end-stage renal disease could only meet death outcome
DESIGN	Interventional: Randomized Clinical Trial (Pragmatic, Crossover design)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Unclear. Patients were randomized based on alternating months. Patients could have been enrolled more than once potentially violating the assumptions of randomization. The authors conducted a sensitivity analysis limited to a patient's first enrollment there was no difference in the primary outcome.
Was randomization concealed?	No. Clinicians were aware of which fluid was intended that month but could chose an alternative fluid at their discretion. 88% of patients received 100% of the intended fluid (92.8% in the saline group and 83.8% in the balanced crystalloid group).
Were patients in the study groups similar with respect to known prognostic factors?	Yes (Table 1). Patients were similar with respective to demographic characteristics, co-morbid conditions, renal function and admitting service.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Clinicians were not blinded to the study group. It is unclear if outcome assessors were blinded. However, the outcome measures were primarily based on objective clinical criteria (death, length of stay) and objective laboratory data (change in serum creatinine). It does not appear that lack of blinding could influence the assessment of these outcomes. The outcome of new renal replacement therapy could potentially be biased by knowledge of the treatment group.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Follow up was until hospital discharge or day 28 of admission (whichever came first).
Were patients analyzed in the groups to which they were randomized?	Yes. The primary analysis was based on the intention to treat principle. The CONSORT diagram is included in Figure S2 in the supplementary materials. 19,949 patients were randomized. 6,602 patients were excluded because they were admitted to the ICU or received less than 500 ml of crystalloid. The remaining 13,347 patients were included in the intention to treat analysis (ITT). 1,567 (11.7%) patients in the ITT analysis did not receive 100% of the intended intervention. The remaining 11,780 who received 100% of the study intervention were included in the per protocol analysis.
Was the trial stopped early?	No. The trial was not stopped early. The authors determined that 14,000 patients would need to be enrolled in order to identify a 0.5-day difference in the primary outcome. 13,247 patients were included in the ITT analysis. The difference found was 0.0 days. An interim analysis mid trial by and independent data safety monitoring board did not recommend stopping the trial or a change in sample size.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 13,347
Saline group: 6,639
Balanced crystalloid group: 6,708 (95.3% Ringer's Lactate, 4.7% Plasmalyte A)

Fluids (Table 2): The mean (1.6 liters) and median volume (1.1 liters) received and proportion of patients receiving more than 2 liters (32%) were similar in both groups

PERCENTAGE OF ALLOCATED FLUID RECEIVED (TABLE 2)

	100% (all)	51-99% (mixed)	1-50% (mixed)	0% (none)
Saline	92.8%	4.1%	2.0%	1.2%
Balanced crystalloid	83.8%	7.7%	3.8%	4.8%
Overall, 88.3% received 100% of the assigned crystalloid				

Electrolytes (Figure 1): Patients in the saline group had a higher chloride and lower bicarbonate that persistent for several days when compared to the balanced crystalloid group. Criteria for hyperchloremia and acidemia were met more commonly in the saline group. The clinical significance of these differences is unclear.

PRIMARY/SECONDARY OUTCOMES: INTENTION TO TREAT ANALYSIS[1] (TABLE 3)

	Balanced (6,708)	Saline (6,639)	Adjusted OR 95% CI
Median Hospital Free Days	25 (22, 26) days	25 (22, 26) days	0.98 (0.92, 1.04)
Major Adverse Kidney Events	315 (4.7%)	370 (5.6%)	0.82 (0.70, 0.95)
Death[3]	94 (1.4%)	102 (1.5%)	0.1% (-0.3, 0.5%)[2]
New renal replacement Rx[3]	0.3%	0.5%	0.2% (0.0, 0,4%)[2]
Serum Cr > 200% Baseline[3]	3.8%	4.5%	0.6% (-0.4, 1.5%)[2]
≥ Stage II Acute Kidney Injury	8.0%	8.6%	0.91 (0.80, 1.03)
In-hospital death	95 (1.4%)	105 (1.6%)	0.88 (0.66, 1.66)

1. Results of the per protocol analysis were similar (Table S5, S6 in Supplementary Appendix)
2. Unadjusted risk differences (RD) calculated from proportions provided (Link: CALCULATOR)
3. Group sizes: Balanced = 6,583, Saline = 6530, excluding patients with ESRD

GREEN = Statistically Significant, RED = Not Statistically Significant

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence intervals for the primary and secondary outcomes are presented in the table above. The large sample size resulted in narrow confidence intervals.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Unclear. This was a large population of adults with a variety of medical reasons for admission at a single US academic medical center. The study results are likely generalizable to patients meeting the studies inclusion and exclusion criteria in similar settings.
Were all patient important outcomes considered?	Yes. However, it would have been helpful to determine if the changes seen in electrolytes resulted in changes in management. The other outcome that I would have liked to see is the proportion of total fluids received throughout the hospital stay that was with the intended study fluid.
Are the likely treatment benefits worth the potential harm and costs?	Ringer's lactate is slightly more expensive than normal saline. Plasmalyte A is considerably more expensive than both. There was no benefit between the treatment groups in the primary outcome of median number of hospital free days in 28 days. Major adverse kidney events within 30 days were more common in the saline group (5.6%) compared to the balanced crystalloid group (4.7%), (Risk difference 0.9%, 95% CI (0.1, 1.6%)). This difference was primarily driven by an increase in creatine (RD 0.7%) and not death (RD 0.1%) or receipt of renal replacement therapy (RD 0.2%). The risk difference corresponds to a number need to treat of 111 (1/0.009). For every 111 patients treated with normal saline when compared to balanced crystalloids, 1 additional patient would have a major adverse kidney event within 30 days.

CLINICAL BOTTOM LINE

BACKGROUND: There has been considerable debate on the effect of the type of crystalloid administered on patient outcomes. Normal saline is the preferred fluid in the US. Normal saline has a saline concentration (154 mmol/L) that is significantly greater than serum (94-111 mmol/L). It is associated with hyperchloremic metabolic acidosis and is associated with kidney injury in animal models. Balanced crystalloid solutions such as Ringer's Lactate (109 mmol/L) and Plasmalyte A (98 mmol/L) more closely approximate the serum saline concentration. The authors hypothesize "that balanced crystalloids would result in earlier hospital discharge and a lower incidence of major adverse kidney events than saline."

CLINICAL QUESTION: In adult patients who are admitted to a non-ICU setting and receive at least 500 ml of intravenous crystalloid in the Emergency Department, do Balanced electrolyte solutions (Ringer's Lactate or Plasmalyte A) when compared to Normal Saline result in a greater number of hospital free days until 28 days after admission and a lower incidence of a major adverse kidney events?

DESIGN/VALIDITY: This was a well-designed single center, pragmatic, randomized clinical trial that included 13,347 patients in the primary intention to treat analysis. Patients receiving greater than 500 ml of intravenous fluids in the ED and who were admitted to a non-ICU setting were included. Patients were randomized on a month by month basis to receive either normal saline or a balanced crystalloid solution (Ringer's lactate or Plasmalyte A). The primary outcome was Hospital free days until day 28. Secondary outcomes were: 1. Major adverse kidney, 2. ≥ Stage II acute kidney injury (KDIGO creatinine criteria) and 3. Death before hospital discharge regardless of length of stay. The study was not blinded. However, the outcome measures were primarily based on objective clinical criteria (death, length of stay) and objective laboratory data (change in serum creatinine). It does not appear that the lack of blinding could influence the assessment of these outcomes.

The primary risk of bias concern is that fluid received after admission were at the discretion of the inpatient treating clinician. Additional outcomes of interest would are the proportion of total fluids received throughout the hospital stay that was with the intended study crystalloid and whether the changes in electrolytes seen resulted in a change in management. There were also a number of potential confounding variables that were not included in the regression analysis that could potentially affect the study outcome measures. Multivariable models were adjusted for age, sex, race, admitting service, and days since trial initiation. Though the study design was interventional, data collection was retrospective from the electronic medical record.

PRIMARY RESULTS: There was no difference between the two groups in the primary outcome of median number of hospital free days within 28 days of admission (both groups: 25 days, IQR (22, 26), adjusted odds ratio 0.98, 95% CI (0.92, 1.04)). Major adverse kidney events within 30 days were more common in the saline group (5.6%) compared to the balanced crystalloid group (4.7%), adjusted odds ratio 0.82, 95% CI (0.70, 0.95). There was no statistically significant difference in the unadjusted risk difference of any of the three components of this outcome based on our calculations. The largest difference was in serum creatine (0.7%) with virtually no difference in deaths (0.1%) of the need for renal replacement therapy (0.2%). However, a baseline creatinine was not available for 35% of participants and had to be estimated. In a subgroup analysis, patients with an initial serum creatinine of greater than 1.5 mg/dl demonstrated the greatest benefit of balanced crystalloids.

There was no difference between the two treatment groups in the proportion of patients sustaining stage II or greater acute kidney injury (adjusted odds ratio 0.91, 95% CI (0.80, 1.03) or the proportion with in-hospital deaths (adjusted odds ratio 0.88, 95% CI (0.66, 1.66)). There was no difference between the results of the intention to treat analysis and per protocol analysis.

PRIMARY/SECONDARY OUTCOMES: INTENTION TO TREAT ANALYSIS[1] (TABLE 3)			
	Balanced (6,708)	Saline (6,639)	Adjusted OR 95% CI
Median Hospital Free Days	25 (22, 26) days	25 (22, 26) days	0.98 (0.92, 1.04)
Major Adverse Kidney Events	315 (4.7%)	370 (5.6%)	0.82 (0.70, 0.95)
Death[3]	94 (1.4%)	102 (1.5%)	0.1% (-0.3, 0.5%)[2]
New renal replacement Rx[3]	0.3%	0.5%	0.2% (0.0, 0,4%)[2]
Serum Cr > 200% Baseline[3]	3.8%	4.5%	0.6% (-0.4, 1.5%)[2]
≥ Stage II Acute Kidney Injury	8.0%	8.6%	0.91 (0.80, 1.03)
In-hospital death	95 (1.4%)	105 (1.6%)	0.88 (0.66, 1.66)
1. Results of the per protocol analysis were similar (Table S5, S6 in Supplementary Appendix) 2. Unadjusted risk differences (RD) calculated from proportions provided (Link: CALCULATOR) 3. Group sizes: Balanced = 6,583, Saline = 6530, excluding patients with ESRD			
GREEN = Statistically Significant, RED = Not Statistically Significant			

Patients in the saline group had a statistically significantly higher sodium and chloride and lower bicarbonate that persistent for several days when compared to the balanced crystalloid group. Criteria for hyperchloremia and acidemia were met more commonly in the saline group. The clinical significance of these differences is unclear.

APPLICABILITY: This was a large population of adults with a variety of medical conditions admitted to a single US academic medical center. Patient specific details were limited due to use of the electronic medical record to collect data retrospectively. The study results are likely generalizable to patients meeting the study's inclusion and exclusion criteria in similar settings. The small proportion of patients receiving Plasmalyte A limits the conclusion that can be made regarding its use.

For every 111 patients treated with normal saline when compared to balanced crystalloids, 1 addition patient would have a major adverse kidney event within 30 days. While this is a large number for the individual patient, the implications may be substantial for the population of patients receiving intravenous crystalloid as a whole.

AUTHOR'S CONCLUSION: "In conclusion, in this pragmatic clinical trial involving noncritically ill adults treated with intravenous fluids in the emergency department, the number of hospital-free days, the primary outcome of the trial, did not differ between patients assigned to balanced crystalloids and those assigned to saline."

POTENTIAL IMPACT: This large, single center study found no difference in the primary outcome of the number of hospital free days between the saline and balanced crystalloid groups. However there was a higher proportion of patients in the saline group with hyperchloremia and acidemia and a higher rate of major adverse kidney events driven primarily by an increase in serum creatine and not in death or need or renal replacement therapy.

This lends support for the use of balance crystalloids particularly in patients with an elevated baseline creatinine and hyperchloremia though there are a number of methodologic concerns that should be taken into account when interpreting the study's result . A multicenter randomized clinical trial including specific data on patient characteristics would further support a change in crystalloid selection.

APPENDIX: FLUID COMPOSITIONS				
	PLASMA	NORMAL SALINE (0.9%)	RINGER'S LACTATE	PLASMALYTE A
pH	7.4	5.5	6.5	6.5
Sodium (Na^+)	142	154	130	140
Chloride (CL^-)	103	154	109	98
Potassium (K^+)	4	0	4	5
Calcium (Ca^{++})	5	0	3	0
Buffer	22-32 (HCO_3)	0	28 (Lactate)	23 (Gluconate) 27 (Acetate)
Osmolality	289	308	273	295

See Also the SMART Trial

Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, Stollings JL, Kumar AB, Hughes CG, Hernandez A, Guillamondegui OD, May AK, Weavind L, Casey JD, Siew ED, Shaw AD, Bernard GR, Rice TW; SMART Investigators and the Pragmatic Critical Care Research Group. Balanced Crystalloids versus Saline in Critically Ill Adults
N Engl J Med. 2018 Mar 1;378(9):829-839., PubMed ID: 29485925

HYPONATREMIA:
ICU MAINTENANCE FLUIDS FLUIDS

In patients 29 days to 18 years who are admitted to a pediatric intensive care unit and require intravenous maintenance fluids does the administration of hypotonic fluids when compared to isotonic fluids increase the risk of hyponatremia?

Anna Joong, M.D., Rebecca Lapat, M.D., Michael Mojica, M.D.
August, 2011

Montañana PA, Modesto I Alapont V, Ocón AP, López PO, López Prats JL, Toledo Parreño JD.

THE USE OF ISOTONIC FLUID AS MAINTENANCE THERAPY PREVENTS IATROGENIC HYPONATREMIA IN PEDIATRICS: A RANDOMIZED, CONTROLLED OPEN STUDY

Pediatr Crit Care Med. 2008 Nov;9(6):589-97.
PubMed ID: 18838929

STUDY DEFINITIONS	
POPULATION	Inclusion: 29-18 years, requiring ICU admission, intravenous maintenance fluids Exclusion: Chronic or acute kidney failure, risk of cerebral edema (diabetic ketoacidosis, head trauma), plasma sodium at admission < 130 mEq/L or > 150 mEq/L, dehydration > 5% of body weight Setting: Single Children's Hospital Pediatric ICU (Spain), 1/2006-3/2006.
INTERVENTION	Isotonic Group: Maintenance fluids with a Sodium concentration of 140 mEq/L and potassium concentration of 15 mEq/L (tonicity 155 mOsm/L).
CONTROL	Hypotonic Group: Maintenance fluids with Sodium concentrations between 20 and 100 mEq/L
CO-INTERVENTIONS	Maintenance fluids determined by Holliday–Segar formula (1st 10 kg = 100 ml/kg/hour, 2nd 10 kg = 50 ml/kg/hour, Every kg > 20 kg = 20 ml/kg/hour) Remaining ionic and glucose (D5) concentrations were the same. Oral tolerance begun and intravenous fluid was interrupted by the same criteria in both groups. Withdrawal Criteria: 1. Sodium < 130 mEq/L or > 150 mEq/L 2. Acquired abnormalities involving sodium or free water kidney excretion (inadequate antidiuretic hormone secretion or diabetes insipidus) 3. Interruption of fluid therapy by order of the physician. Sodium, glucose, blood pressure at admission, 6 and 24 hours Plasma creatinine, urine specific gravity, electrolytes at 6 hours
OUTCOME	Primary Outcome: Percentage of hyponatremia acquired during treatment at 6 and 24 hours Hyponatremia: < 135 mEq/L, moderate < 130 mEq/L, severe 125 mEq/L Hypernatremia: > 145 mEq/L Hypertension: Average systolic or diastolic blood pressure ≥ 95th percentile for gender, age, and height on three measurements.
DESIGN	Interventional: Randomized controlled trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized using computer generated blocks to ensure equal group size
Was randomization concealed?	Unclear. The authors state that “To ensure concealment two block sizes are used” but it is uncertain how this would conceal allocation to the treatment groups.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Table 1. Patients are roughly similar in all the parameters measured.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study was not blinded though the primary outcome of hyponatremia is objective and should not be influenced by the lack of blinding.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	No. Follow up was not complete. 19/122 (16%) of the patients were lost at the 6-hour outcome and an additional 57/122 (47%) were lost at the 24-hour outcome. Only 35% of the patients competed all phases. Equal number were lost in the 2 study groups. Patients who left the study prior to its completion were similar in baseline characteristics to those who remained. Most left because intravenous fluids were no longer needed or emergency surgery was required.
Were patients analyzed in the groups to which they were randomized?	Yes. The analysis was based on an intention to treat principle. Patients leaving the study at 6 and 24 hours were included in the analysis. A per protocol analysis was not completed.
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

	HYPOTONIC	ISOTONIC	TOTAL
Admission	63	59	112
6 hours	52	51	103
24 hours	23	23	46

Average Na+ on admission: 137 meq/L

6 HOURS (TABLE 4)

	HYPOTONIC	ISOTONIC	P value
N	52	51	
Serum Sodium	136.4 ± 6.8	137.0 ± 3.7	NS
Hyponatremia	20/63 (31.7%)	15/59 (25.4%)	NS
Moderate	4/63 (6.3%)	0/59 (0%)	NS
Severe	4/63 (6.3%)	0/59 (0%)	NS

There was a statistically significant lower mean sodium in the subgroup of patients with abdominal surgery in the hypotonic fluids group (134 meq/l) than the isotonic fluids group (136 meq/l). A 2 meq/l difference is unlikely to have clinical significance.

24 HOURS (TABLE 5)

	HYPOTONIC	ISOTONIC	P value
N	23	23	
Serum Sodium	136.2 ± 5.2	138.9 ± 3.7	0.02
Hyponatremia	13/63 (20.6%)	3/59 (5.1%)	0.02
Moderate	3/63 (4.8%)	0/59 (0%)	NS
Severe	0/63 (0%)	0/59 (0%)	NS

Risk Hyponatremia Isotonic: 3/59 = 5.1%
Risk Hyponatremia Hypotonic: 13/63 = 20.6%
Relative Risk (Isotonic/Hypotonic) = 5.1/20.6 = 0.24, 95% CI (0.08, 0.75)
Absolute Risk Difference = Hypotonic – Isotonic
= 20.6% - 5.1% = 15.5%, 95% CI (4.1, 27.8%)
(The authors specified a 25% difference in the rate of hyponatremia as clinically significant in their sample size determination. Required sample size was 122 patients.)
No cases of hypernatremia, hypertension or phlebitis were seen in the isotonic group

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See confidence intervals for the risk difference and relative risk for hyponatremia at 24 hours are presented above. The confidence intervals are very wide (imprecise) due to the small sample size.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Unclear. The only patient characteristics provided were age, gender, type of diagnosis and that they were admitted to the ICU. Approximately, 75% of patients had a primarily surgical diagnosis.
Were all patient important outcomes considered?	No. Mostly surrogate laboratory markers of disease probability were provided and not actual measures of cerebral edema or seizures. The hyponatremic group received fluids with between 20 and 100 meq/liter. It would have been helpful to determine if there was a dose response relationship in this group. The study was not powered to determine rare adverse events in the isotonic fluid group nor did it address the issue of hypochloremic acidosis in this isotonic fluid group.
Are the likely treatment benefits worth the potential harm and costs?	There was a statistically significant decrease in serum sodium in the hypotonic fluid group when compared to the isotonic group at 24 hours. This difference was modest and probably not of clinical significant. Number needed to treat (NNT) = 1/(absolute risk difference) = 1/0.155 = 6.5. 6.5 patients would need to be with isotonic fluids to prevent 1 additional case of hyponatremia.

CLINICAL BOTTOM LINE

BACKGROUND: Historically hypotonic fluids have been used for maintenance hydration in children. Many conditions requiring admission may stimulate antidiuretic hormone secretion. Children with such conditions have a limited ability to excrete free water and may be at increased risk for hyponatremia and its complications when given hypotonic fluids. For this reason, many authors have recommended the use of isotonic fluids as maintenance therapy for pediatric patients.

CLINICAL QUESTION: In patients 29 days to 18 years who are admitted to a pediatric intensive care unit and require intravenous maintenance fluids does the administration of hypotonic fluids when compared to isotonic fluids increase the risk of hyponatremia?

DESIGN/VALIDITY: The study was well-designed and included 112 patients at enrollment. There are some validity concerns. It is unclear why the isotonic fluid group received maintenance fluids with a varying concentration of sodium (between 20 and 100 mEq/L). It would have been helpful to determine if there was a dose response relationship in the hypotonic fluids group. The primary concern is that only 35% of the patients completed the study though those exiting the study early were similar in both groups and similar to the initial group of patients. Patients who left the study early did so primarily because they no longer needed intravenous fluids or required emergency surgery. The authors only assessed laboratory outcomes and was not powered to identify rare clinical adverse events in the hypotonic group (cerebral edema, seizures)

PRIMARY RESULTS: The study demonstrated a modest decrease in the proportion with hyponatremia in the hypotonic fluids group at 24 hours (Absolute Risk Difference = Hypotonic group (20.6%) - Isotonic group (5.1%) = 15.5%). The authors specified a 25% difference in the rate of hyponatremia as clinically significant in their sample size determination. There was also a statistically significant lower serum sodium in the hypotonic group (136.2 ± 5.2 meq/L) than in the isotonic group (138.9 ± 3.7 meq/L) at 24 hours though the absolute difference in serum sodium (2.7 meq/L) is likely not clinically significant. There were no complications such as hypertension, or hypernatremia associated with the use of isotonic solutions. However, there was no assessment for hyperchloremic, metabolic acidosis in this group.

APPLICABILITY: The only patient characteristics provided were age, gender, type of diagnosis and that they were admitted to the ICU. Approximately, 75% of patients had a primarily surgical diagnosis (head, thorax, abdomen or cardiac) so the generalizability to non-surgical ICU patients is unclear.

AUTHOR'S CONCLUSION: "In conclusion, this study demonstrates that isotonic fluids prevent iatrogenic hyponatremia without inducing a higher incidence of side effects. Therefore, these would be the maintenance fluids that should be selected for patients with no excessive and continuous loss of free water or previous plasma sodium abnormalities. The traditional recommendation by Holliday and Segar should be reconsidered, and the amount of sodium administered with regards to the volume of the infusion and not per kilogram of weight of the children should be assessed. Furthermore, the higher risk of hyponatremia in patients undergoing abdominal surgery and receiving hypotonic solutions should be confirmed, and the isonatremic dilution to be used to minimize the risk of hyperchloremic acidosis should be determined."

POTENTIAL IMPACT: The study demonstrated a small but statistically significant increased risk of hyponatremia in those receiving hypotonic maintenance solutions at 24 hours. The small difference in sodium levels are likely not clinically significant and no clinical symptoms of hyponatremia were reported. There were no complications associated with the use of isotonic maintenance fluids thought the possibility of hyperchloremic metabolic acidosis was not assessed. Further studies, including non-surgical patients with a larger sample size to assess important subgroups (such as those known to be a risk for the syndrome of inappropriate antidiuretic hormone (SIADH) secretion) are needed before definitive recommendations for a change from isotonic to hypotonic maintenance solutions can be made.

HYPONATREMIA:
MAINTENANCE INTRAVENOUS HYDRATION

In children undergoing intravenous hydration with hypotonic maintenance fluids what factors as associated with the development of hyponatremia?

Jennifer Curran, M.D., Jeffrey Fine, M.D.
January 2005

Hoorn EJ, Geary D, Robb M, Halperin ML, Bohn D.

ACUTE HYPONATREMIA RELATED TO INTRAVENOUS FLUID RESUSCITATION IN HOSPITALIZED CHILDREN: AN OBSERVATIONAL STUDY

Pediatrics. 2004 May;113(5):1279-84.,
PubMed ID:15121942

STUDY DEFINITIONS	
POPULATION	Inclusion: Admitted patients who had at least 2 sodium levels obtained. One at the time of admission and a second within the next 48 hours Exclusion: Patients with a reason for a shift of water from the intracellular fluid to the extracellular fluid (ECF) compartment (e.g., hyperglycemia) and those given hypertonic Mannitol. Setting: Single Children's Hospital (Canada), 11/2000-2/2001
CASE	Patients with hospital-acquired hyponatremia (< 136 meq/L)
CONTROL	Age and gender matched patients who did not develop hyponatremia
OUTCOME	Risk factors for acute hyponatremia 1. Volume and tonicity of oral and intravenous fluid intake (compared to recommendations for maintenance fluid) 2. Data suggestive of a contracted extracellular fluid volume: Low blood pressure, rapid heart rate, reduced capillary refill time and replacement fluids provided Possible central nervous system symptoms of acute hyponatremia: Headache, nausea, vomiting, seizures, and changes in mental status
DESIGN	Observational: Retrospective Case-control

HOW SERIOUS WAS THE RISK OF BIAS? (CASE-CONTROL)	
DID THE CASES AND CONTROLS HAVE THE SAME RISK FOR BEING EXPOSED IN THE PAST?	
Were cases and controls similar with respect to the indication or circumstances that would lead to exposure? (or did statistical adjustments address the imbalance).	Unclear. The demographics of the two groups are similar except there were more surgical patients in the hyponatremia group. It is not clear whether the control and study patients were similar in terms of disease severity or specific type of disease processes. No regression or sub-analyses were described.
Were the circumstances and methods for determining exposure similar for cases and controls?	Yes. Serum sodium was measured and defined as abnormal in the same way in both groups. It is unclear what the indications for a repeat sodium level were. Patients who were in some way could have been more likely to have a repeat sodium level (selection bias). The patients may have varying reasons for having sodium levels re-checked. The patients in the control group were only matched to the study group by age and gender. It is possible that patients developed hyponatremia shortly after discharge or were missed because repeat levels were not obtained.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

N= 432 patients with 2 Na^+ measurements,

Cases: 97 (22.4%) with Na^+ < 136 meq/L
62 Hyponatremic on presentation
12 remained hyponatremic
45 hyponatremia resolved
5 hyponatremia resolved then recurred*
35 developed hyponatremia after presentation*
*acquired hyponatremia = 40 (35 + 5)

Controls: 335 (77.6%) with Na^+ ≥ 136 on both samples

Acquired Hyponatremia over 19 ± 10 hours (n=40)
Pre: 139 ± 3 meq/L
Post: 133 ± 2 meq/L
Mean Difference: 6 ± 3 meq/L

Volume of Fluid Received
Case: 98 ± 77 ml/hour
Control: 47 ± 46 ml/hour
Mean Difference: 51 ml/hour ($p < 0.001$)

More Than Recommended Maintenance Fluids
Case: 73%
Control: 23%
Risk Difference: 50% ($p < 0.001$)

Odds Ratio (> Maintenance/≤ Maintenance)
OE = 8.8, 95% CI (3.8, 20.6).

There were more surgical patients in the group that developed hyponatremia: 16% vs 5% ($p = 0.04$)

Symptoms possibly related to hyponatremia
Significantly higher rate of nausea (27% vs 8%) and vomiting (68% vs 41%) in the hyponatremia group.
No difference in the rate of headache, seizures or altered mental status.

HOW PRECISE IS THE ESTIMATE OF THE RISK?

Confidence intervals around the differences between the case and control groups were not presented.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Unclear. These were inpatients with a variety of disease processes. A narrower population, examined prospectively would have allowed greater generalizability.
Was follow-up sufficiently long?	Follow-up was not attempted. The indications for a second sodium level were not provided so that there is a possibility of selection bias. It is also possible that patients developed hyponatremia shortly after discharge or were missed because repeat levels were not obtained.
Is the exposure similar to what might occur in my patient?	The exposure, receipt of hypotonic fluids, may occur at our institution. The study institution commonly used 3.3% Dextrose in 0.3% NaCl, a hypotonic solution, for maintenance fluids
What is the magnitude of the risk?	Patients receiving more than maintenance fluids were 8.8 times more likely to developed hyponatremia (OR = 8.8, 95% CI (3.8, 20.6)). There also appears to be a higher risk of hyponatremia if children are hydrated with higher rates of hypotonic fluid, especially after surgery or if deficits have not been replaced with isotonic fluid.
Are there any benefits that offset the risks associated with exposure?	The clinical relevance of the hyponatremia that developed in the study is unclear. The average decrease in sodium was to a level of 133 meq/L. Clinical manifestations of hyponatremia are typically associated with a level of < 130 meq/L. The potential benefit of isotonic fluids must be assessed against the risk of hyperchloremic metabolic acidosis.

CLINICAL BOTTOM LINE

BACKGROUND: Historically hypotonic fluids have been used for maintenance hydration in children. Many conditions requiring admission may stimulate antidiuretic hormone secretion. Children with such conditions have a limited ability to excrete free water and may be at increased risk for hyponatremia and its complications when given hypotonic fluids. For this reason, many authors have recommended the use of isotonic fluids as maintenance therapy for pediatric patients.

CLINICAL QUESTION: In children undergoing intravenous hydration with hypotonic maintenance fluids what factors as associated with the development of hyponatremia?

DESIGN/RISK OF BIAS: This is a retrospective, observational study which consists of both a retrospective case series and a case-control study. Of 432 patients, 97 (22.4%) had hyponatremia. 62 at initial presentation (n=62) and 35 developed hyponatremia after presentation. 335 (77.6%) age and gender matched patients served as a control group.

Several potential biases may impact the validity of the study's conclusions. There are numerous likely risk factors for hyponatremia that may not have been accounted for (insensible losses, disease processes associated with the syndrome of inappropriate antidiuretic hormone secretion). It would have been useful to see a subset analysis for different types of patients (for example, surgical, neurological disease) to help determine whether hypotonic fluids were an independent predictor for the development of hyponatremia. In addition, not all patients had a second serum sodium measured introducing the possibility of selection bias.

PRIMARY RESULTS: In those who developed hyponatremia after admission, sodium levels fell from an average of 139 ± 3 meq/L to 133 ± 2 meq/L, a decrease by 6 ± 1 meq/L within 19 ± 10 hours. It is unclear is this is clinically relevant. It is thought that patients typically develop clinical manifestations of hyponatremia when sodium drops below 130 meg/L. Patients who developed hyponatremia were significantly more likely to receive a higher volume of fluids (Case: 98 ± 77 ml/hour, Control: 47 ± 46 ml/hour, Difference: 51 ml/hour ($p < 0.001$) and receive more than recommended maintenance fluids (Case: 73%, Control: 23% Difference: 50% ($p < 0.001$)). Patients receiving more than maintenance fluids were 8.8 times more likely to developed hyponatremia (Odds Ratio = 8.8, 95% CI (3.8, 20.6). For 16 patients of the 37 in the hyponatremia group, the investigators were not able to explain the decrease sodium by the amount of free water given to the patient (? SIADH).

Patients who developed hyponatremia had significantly higher rate of nausea (27% vs 8%) and vomiting (68% vs 41%). It is unclear if this association represents a causal relationship. Patients who were vomiting could have received more fluids. There was no difference in the rate of headache, seizures or altered mental status.

Finally, it is unclear whether the volume or the tonicity or of the fluids received or both contributed to the development of hyponatremia.

APPLICABILITY: The variability of the patients included make it difficult to generalized the study's findings to specific risk groups such as those undergoing surgery and those with an increased risk of SIADH. A narrower population or larger study allowing for subgroup analysis that was examined prospectively would have allowed greater generalizability.

AUTHOR'S CONCLUSION: "In conclusion, this study demonstrates that isotonic fluids prevent iatrogenic hyponatremia without inducing a higher incidence of side effects. Therefore, these would be the maintenance fluids that should be selected for patients with no excessive and continuous loss of free water or previous plasma sodium abnormalities. The traditional recommendation by Holliday and Segar (1) should be reconsidered, and the amount of sodium administered with regards to the volume of the infusion and not per kilogram of weight of the children should be assessed. Furthermore, the higher risk of hyponatremia in patients undergoing abdominal surgery and receiving hypotonic solutions should be confirmed, and the isonatremic dilution to be used to minimize the risk of hyperchloremic acidosis should be determined."

POTENTIAL IMPACT: The results of this study suggest that physicians should be careful in hydrating children. It is important to calculate deficits and replace them with isotonic fluids before infusing hypotonic fluids. There may be a risk of symptomatic hyponatremia from infusion of hypotonic fluids, especially at rates higher than maintenance and in those undergoing surgery.

ENVIRONMENTAL INJURIES

1. Esophageal Coins: Spontaneous Passage: Peds. 2005
2. Esophageal Impaction: Glucagon: Pharmacotherapy. 2019

ESOPHAGEAL COINS: SPONTANEOUS PASSAGE

In an asymptomatic child with an esophageal coin does a period of observation compared to relatively immediate endoscopic removal result in an increased rate of spontaneous passage?

Eric Weinberg, M.D., Michael Tunik, M.D.
December, 2005

Waltzman ML, Baskin M, Wypij D,
Mooney D, Jones D, Fleisher G.

A RANDOMIZED CLINICAL TRIAL OF MANAGEMENT OF ESOPHAGEAL COINS IN CHILDREN

Pediatrics. 2005 Sep;116(3):614-9.
PubMed ID: 16140701

STUDY DEFINITIONS	
POPULATION	Inclusion: < 21 years, esophageal coin on XRAY Exclusion: Prior tracheal/esophageal surgery, presence of more than minimal symptoms (respiratory distress, drooling, or choking), ingestion occurring > 24 hours earlier, inability to ascertain the time from ingestion. Setting: Single Pediatric Emergency Department, 3/2001-12/2003
INTERVENTION	Observation: Admitted to hospital, continuous cardiac monitoring with pulse oximetry, intravenous fluids, NPO, repeat radiographic evaluation 16 hours after ingestion, endoscopic removal of any coins that failed to pass spontaneously into the stomach.
CONTROL	Removal: General pediatric surgeon or otorhino-laryngologist, extracted the coin under general anesthesia by rigid esophagoscopy, as soon as operating room available. A second XRAY obtained to verify coin retention in the esophagus in transfer from another institution with a radiograph or a delay in endoscopy > 2 hours
OUTCOME	Primary Outcome: Proportion of patients requiring endoscopy Secondary Outcomes: 1. Length of stay 2. Complications: Choking, vomiting, respiratory distress, hypoxia, coin translocation to the trachea, esophageal perforation (hospital records reviewed to ensure no unreported complications) 3. Relationship between coin size (type) and spontaneous passage 4. Relationship between esophageal coin location and spontaneous passage
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized to endoscopy versus observation though the method of randomization was not stated. Patients in the endoscopy group were non-randomly assigned (even versus odd days) to either a pediatric surgeon or a pediatric ENT.
Was randomization concealed?	Unclear. Sealed envelopes were used to assign patients.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Age, gender, race, or coin type were similar. There was a difference in coin location with the observation group having more coins in upper esophagus. This could potentially bias the study results against observation if coins in the upper esophagus are less likely to pass spontaneously. Logistic regression was completed to account for differences. Importantly, the duration from ingestion to presentation for each group was not presented.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study design precluded blinding. Knowledge of the study group however does not appear to have the potential to bias the assessment of the primary outcome of spontaneous passage.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. All patients who entered the study were accounted for at completion of study.
Were patients analyzed in the groups to which they were randomized?	Yes. In intention to treat analysis was utilized. No patients switched groups during the duration of the study. If patients in the endoscopy group underwent spontaneous passage they were still analyzed within the same group. Similarly, none of the patients in the observation group required earlier endoscopy secondary to complications.
Was the trial stopped early?	No. The trial was not stopped early.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Primary Outcome: Need for endoscopy
Observation group: 23/30 (77%)
Endoscopy group: 21/30 (70%)
Absolute Risk Difference: - 6.7% 95% CI (-1.9, 4.9%)
The authors specified a difference of 34% (10% vs 44%) or 31% (5% vs 36%) to be clinically significant in their sample size determination.

Secondary Outcomes: Length of stay
Observe 19.4 hours,
Endoscopy 10.7 hrs.
Mead Difference: 8.7 hours, 95% CI (4.2-8.7 hours)

Secondary Outcomes: Complications
Observe 0 %
Endoscopy 0%
Absolute Risk Difference: 0%, 95% CI (0, 5%)

Regression: Independent predictors of passage
Coin location (proximal/distal): OR 2.44, 95% CI (1.05,5.57)
Not Predictive: Age, gender, coin type, coin size

Time to passage: Majority within 6-8 hours, all by 19 hours.

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See confidence intervals above

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patients?	Yes. Study patients were relatively similar to our population with the exception of ethnicity. Because of exclusion criteria, data can only be applied to asymptomatic patients with no history of esophageal or tracheal surgery, with known coin ingestion < 24 hours.
Were all patient important outcomes considered?	Yes. Though a cost analysis of the two strategies was not included.
Are the likely treatment benefits worth the potential harm and costs?	The primary benefit of observation is the avoidance of anesthesia/endoscopy and the potential complication of the procedure. The primary risk in observation in this study was an increased length of stay. The sample size was not adequate to assess for the possibility or rare complications.

CLINICAL BOTTOM LINE

BACKGROUND: Children, particularly toddler, ingest a variety of foreign bodies for reasons only known only to them. Many of the foreign bodies are coins and many of those coins lodge in the esophagus. The approach to esophageal coins has traditionally been to remove them endoscopically as soon as possible though evidence to support this approach is lacking. The ability to determine which coins will pass spontaneously and the time frame for passage without complications would allow many children to avoid sedation and endoscopic removal of the coin.

CLINICAL QUESTION: In an asymptomatic child with an esophageal coin does a period of observation compared to relatively immediate endoscopic removal result in an increased rate of spontaneous passage?

DESIGN/VALIDITY: This study attempted to determine if a period of observation could be employed to decrease the rate of endoscopic removal. In addition, they sought to examine clinical and radiographic predictors of spontaneous passage of esophageal coins. This is a well-designed study that included 60 patients in the primary analysis. Patients were randomized to an observation The variability in the early endoscopy group of who received a second XRAY may limit the validity of the findings.

PRIMARY RESULTS: Approximately, 25-30% of patients will potentially avoid endoscopy with this strategy (Endoscopy rate: Observation group: 23/30 (77%), Endoscopy group: 21/30 (70%), Absolute Risk Difference: - 6.7% 95% CI (-1.9, 4.9%). The authors specified a difference of 34% (10% vs 44%) or 31% (5% vs 36%) to be clinically significant in their sample size determination. There were no complications associated with observation though the small sample size of this study may miss rare complications.

APPLICABILITY: The study's results can likely be generalized to those meeting inclusion and exclusion criteria. Results can only be applied to asymptomatic patients with no history of esophageal or tracheal surgery and with a known coin ingestion of less than 24 hours. The results cannot be extrapolated to non-coin esophageal foreign bodies and definitely not to button batteries. A careful radiologic analysis should be undertaken to distinguish between a coin and a button battery if an observation approach is considered.

AUTHOR'S CONCLUSION: "Because 25% to 30% of esophageal coins in children will pass spontaneously without complications, treatment of these patients may reasonably include a period of observation, in the range of 8 to 16 hours, particularly among older children and those with distally."

POTENTIAL IMPACT: In asymptomatic pediatric patients with an esophageal coin ingestion of less than 24 hours' duration and no history of esophageal or tracheal surgery, it appears feasible to observe for spontaneous passage. The location of the coin may impact the clinical decision-making process with distal coins having a higher rate of spontaneous passage. A larger sample size would be required to assess for the possibility of rare complications with either the observation or immediate endoscopy approach. Alternative strategies such Foley catheter removal and esophageal bouginage were not assessed though these techniques are rarely used currently.

ESOPHAGEAL IMPACTION: GLUCAGON META-ANALYSIS

In patients with an esophageal foreign body or food impaction, does Glucagon aid in disimpaction or passage of the foreign body, when compared with control or placebo?

Ellen Duncan MD PhD, Rebecca Burton MD
August 6, 2019

Peksa GD, DeMott JM, Slocum GW, Burkins J, Gottlieb M.

GLUCAGON FOR RELIEF OF ACUTE ESOPHAGEAL FOREIGN BODIES AND FOOD IMPACTIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Pharmacotherapy. 2019 Apr;39(4):463-472.
PubMed ID: 30779190

STUDY DEFINITIONS	
POPULATION	Inclusion Criteria: Retrospective, prospective observational, and randomized control studies Studies had to have comparator group (control or placebo). Exclusion Criteria: Case reports, case series, and abstracts only. Setting: US (n=4), Sweden (n=1), ED (n=4), ENT Clinic (n=1) Search ending 3/2018
INTERVENTION	Glucagon 1mg per dose (most frequent), allowing for repeat dosing, pediatric dosing of 0.1 mg/kg with a maximum of 1 mg
CONTROL	Placebo (2) and control (3)
CO-INTERVENTIONS	Studies used either Glucagon alone (1), or with 2-3 oz of water (1), diazepam (1) or a benzodiazepine or nitroglycerin to a proportion of patients (2)
OUTCOME	Primary Outcome: Treatment success as defined by original study Subjective symptom relief (4 adult studies) Confirmation of passage via radiographic imaging (1 pediatric study) Secondary: Rate of overall adverse events Rate of vomiting Time to relief of impaction
DESIGN	Meta-analysis: RCT and observation cohort studies

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review explicitly address a sensible clinical question?	Yes. This is a treatment modality suggested to us by consult services, and it is useful to determine whether studies have shown it to be effective. It is unclear if food impaction in adults and foreign bodies in children would have the same response to Glucagon and should be analyzed together in a meta-analysis.
Was the search for relevant studies detailed and exhaustive?	Yes. Search conducted in conjunction with a medical librarian and included PubMed, CINAHL, Latin American and Caribbean Health Sciences Literature (LILACS), Scopus, Cochrane Database of Systemic Reviews, and Cochrane Central Register of Controlled Trials. It is unclear why EMBASE was not included. Bibliographies of identified articles were searched for potentially missed articles. The search was not limited by language and the search strategy is included in the appendix. Searches were from database inception until March 2018. Funnel plot (Figure 3) and Eggers test did not reveal evidence of publication bias. Two independent investigators assessed study abstracts for inclusion, then reviewed full manuscripts. Discrepancies were settled by a third party.
Was the risk of bias of the primary studies assessed?	Yes. Quality of studies was assessed by two independent investigators using the Cochrane Risk of Bias Tool (RCT) or modified Cochrane Risk of Bias Tool (Observational studies) (Table 2 and Table 3). and mediated by a third party when necessary. Studies were also assessed for evidence quality using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach (Table 4). It is unclear why they used both tools. All 5 studies were described as at overall low risk of bias. One RCT was at moderate risk of bias for blinding and all retrospective studies had moderate risk of bias for confounding.
Were the selection and assessment of studies reproducible?	Unclear. Interrater reliability for study inclusion and quality were not presented.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

As shown in the forest plot for the primary outcome in Figure 2, there is overlap between the confidence intervals between all of the different studies, indicating that results were mostly similar,

An I^2 = 14% indicates low heterogeneity between study results.

WHAT ARE THE OVERALL RESULTS OF THE REVIEW?

N= 5 studies (US (4), Sweden (1)) including 23 study sites
Design: RCT with placebo (2), retrospective cohort with a control group (3)
Location: ED (4) ENT clinic (1)
N = 1,185 patients with a mean patient age that ranged from 5.1-59.5 years

Primary Outcome: Clinical signs of relief (4), XRAY passage (1)
Glucagon: 213/706 (30.2%)
Control or Placebo: 158/479 (33.0%)
Odds Ratio: 0.90, 95%CI (0.69, 1.17) (Figure 2)
Risk Difference: 2.8%, 95% CI (-2.5, 8.2%)

Secondary Outcomes
Overall Adverse effects (Figure 4)
Glucagon: 24/706 (15%)
Control or Placebo: 0/479 (0%)
Odds Ratio: 0.18, 95% CI (0.03, 0.33)

There was no difference in the rate of vomiting (Figure 5)
Only 1 study assessed time to relief of impaction and there was a non-significant difference between the glucagon and control groups.

DID THE REVIEW ADDRESS CONFIDENCE IN EFFECT ESTIMATES?

The aggregated odds ratio of 0.90 had a confidence interval of 0.69 to 1.17 (Figure 2). This is fairly wide. The upper limit of the confidence interval is very close to 1. A larger sample size may have resulted in a statistically significant difference in favor of the control group. The small absolute difference of 2.8% would not be clinically significant. Since this confidence interval crosses 1, there is no statistically significant difference between glucagon and control group.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were all patient-important outcomes considered?	Yes. Treatment success, as well as time to disimpaction, vomiting, and adverse effects, were considered.
Are any postulated subgroup effects credible?	There were no postulated subgroup effects discussed. It would be useful to see subgroup analyses of foreign body (pediatrics) versus food impaction (adult), and to look for efficacy of Glucagon based on the level of the esophagus involved (thoracic inlet, aortic arch, lower esophageal sphincter).
What is the overall quality of the evidence?	The authors determined an overall low risk of bias, though one RCT was at moderate risk of bias for blinding and all retrospective studies had moderate risk of bias for confounding.
Are the benefits worth the costs and potential risks?	There was no apparent benefit of giving glucagon, in terms of disimpaction success, and there were more adverse events.

CLINICAL BOTTOM LINE

BACKGROUND: Esophageal foreign bodies are common in pediatric and adult populations. High risk pediatric foreign bodies include disc batteries and more than one magnet (or 1 magnet and a metallic foreign body). These should undergo endoscopic removal in a timely fashion. In order to avoid endoscopic removal, which is invasive, requires sedation and increases the risk of aspiration, some subspecialty consultants have suggested a trial of Glucagon. Glucagon is thought to increase esophageal peristalsis, decrease esophageal transit time and decrease tone of the lower esophageal sphincter.

CLINICAL QUESTION: In patients with an esophageal foreign body or food impaction, does Glucagon aid in disimpaction or passage of the foreign body, when compared with control or placebo?

DESIGN/RISK OF BIAS: This was a systematic review and meta-analysis including 5 studies (randomized clinical trial (2) and observation studies with a comparator group (3). It is not clear that the single pediatric study with esophageal coins should have been included in this primarily adult population with esophageal food impaction. The search was comprehensive and well documented without evidence of publication bias though the European database EMBASE was not searched. The individual studies were assessed as low risk of bias. It would have been helpful to include inter-rater reliability for the 2 investigators assessment of study inclusion and quality. The effect of the various co-interventions used in 4 of the 5 studies cannot be assessed.

PRIMARY RESULTS: There was no difference between the Glucagon group 30.2% (213/706) and the Control group 33.0% (158/479) in terms of disimpaction or passage of foreign body (Odds Ratio: 0.90, 95%CI (0.69, 1.17). There was a higher rate of overall adverse effects in the Glucagon group (24/706 (15%)) compared to the control group (0/479 (0%)), Risk Difference: 18%, 95%CI (3, 33%). These adverse effects were generally mild and self-limited. There was no difference in the rate of vomiting. The time to relief of impaction was only assessed in 1 study there was a nonsignificant difference between the glucagon and control groups. The analysis did not account for co-interventions did not account for the location in the esophagus of the impaction/foreign body distal impaction is more likely to resolve spontaneously).

APPLICABILITY: Given that we see both pediatric and adult patients, we are likely to see patients with the chief complaint of esophageal foreign body. Additionally, 4 of the 5 studies were conducting in the ED setting, with 1 of the 4 being conducted in a pediatric ED. The patients in this study are in some part likely to be similar to our patients. However, this meta-analysis included only 14 pediatric patients with esophageal foreign bodies so that the study results should not be generalized to this population.

AUTHOR'S CONCLUSION: "Glucagon was not associated with a difference in treatment success but had a higher rate of adverse events. This study does not support the use of glucagon for the treatment of esophageal foreign body and food impaction. Further controlled studies with adequate power to assess adverse events are needed to confirm the efficacy of glucagon. "

POTENTIAL IMPACT: Glucagon is not a commonly administered medicine in the pediatric ED, and this meta-analysis in unlikely to change that. This study provides us with data to share with our specialty colleagues regarding Glucagon's lack of efficacy in adults with esophageal food impaction and the potential for adverse events. Conclusions regarding the pediatric population with esophageal foreign bodies cannot be made based on this study.

GASTRO ENTEROLOGY

1. Gastroenteritis: Apple Juice Rehydration: JAMA 2016
2. Gastroenteritis: Dehydration Rule: Pediatrics 1997
3. Gastroenteritis: IV Dextrose: Ann Emerg Med. 2013
4. Gastroenteritis: Nasogastric Rehydration: Ped. 2011
5. Gastroenteritis: Oral Ondansetron: N Engl J Med. 2006
6. Gastroenteritis: Oral Rehydration Therapy: Ped. 2005
7. Gastroenteritis: Probiotics vs Placebo: NEJM 2018

GASTROENTERITIS:
APPLE JUICE REHYDRATION

In pediatric patients with mild dehydration due to acute gastroenteritis is a regimen of ½ strength apple juice in the emergency department followed by preferred fluids at home non-inferior to an electrolyte maintenance solution in both settings in reducing treatment failures?

Svetlana Dani, M.D., Jason Choi, M.D., Michael Mojica, M.D.
August 9, 2016

Freedman SB, Willan AR, Boutis K, Schuh S.

EFFECT OF DILUTE APPLE JUICE AND PREFERRED FLUIDS VS ELECTROLYTE MAINTENANCE SOLUTION ON TREATMENT FAILURE AMONG CHILDREN WITH MILD GASTROENTERITIS: A RANDOMIZED CLINICAL TRIAL

JAMA. 2016 May 10;315(18):1966-74.
PubMed ID: 27131100

STUDY DEFINITIONS	
POPULATION	Inclusion: 6-60 months. ≥ 8 kg, acute gastroenteritis (≥ 3 episodes of vomiting and/or diarrhea in the past 24 hours), duration of < 96 hours. Minimal dehydration defined as ≤ 5 points on an 8 point dehydration scale (see Appendix) and a capillary refill < 2 seconds Exclusion: Chronic gastrointestinal disease, diabetes, inborn errors of metabolism, prematurity with corrected age < 30 weeks, bilious vomiting, hematochezia, hematemesis, acute abdomen and need for intravenous fluids Setting: Single Children's Hospital (Toronto). Oct-April 2010-2015
INTERVENTION	ED: ½ strength apple juice Home: Replace losses (2 ml/kg per vomit, 10 ml/kg per diarrhea) with ½ strength apple juice or other preferred fluids
CONTROL	ED: Electrolyte maintenance solution (EMS): apple flavored, sucralose sweetened Home: Replace losses (2 ml/kg per vomit, 10 ml/kg per diarrhea) with EMS
CO-INTERVENTIONS	ED: Fluids at 5 ml Q2-5 minutes Given 2 liters of study solution upon discharge Non-experimental ED treatments (e.g. Ondansetron) per institution guidelines Phone follow up Q24 hours until symptom resolution, 72-84 hour revisit
OUTCOME	Primary Outcome: Treatment Failure: Any 1 within 7 days 1. Hospitalization or Intravenous rehydration 2. Subsequent unscheduled MD visit 3. Protracted Symptoms: ≥ 3 episodes of vomiting or diarrhea in a 24 hour period occurring > 7 days after index visit 4. MD request for other treatment (cross over) at index visit 5. ≥ 3% weight loss or dehydration scale score ≥ 5 Analyzed both compositely and as individual variables Secondary Outcomes: IV hydration or hospitalization within 7 days Frequency of vomiting and diarrhea % change in weight at 72-84 hour revisit
DESIGN	Interventional: Randomized clinical trial (non-inferiority hypothesis)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes, patients were randomized in computer generated blocks of 8.
Was randomization concealed?	Yes. Research and pharmacy staff who were not responsible for patient selection, enrollment or treatment allocation, created and stored the randomization table. Treatment assignments provided in opaque sealed envelopes. Color matched fluids prepared in identical opaque bottles.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. See Table 1. Of note only 42% had a history of diarrhea while 94% had a history of vomiting. 68% had no evidence of dehydration. Approximately 2/3 received ondansetron
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded	ED MD's and RN's were blinded to study group, Outcome assessors were blinded to study group. Parents were able to un-blinded at home if they ran out of study fluid.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDY'S CONCLUSION?	
Was follow-up complete?	Yes. See Figure 1. Of the 647 patients enrolled only 3 patients were excluded from the primary analysis because they did not follow up (1 in the AJ/Preferred group and 2 in the EMS group)
Were patients analyzed in the groups to which they were randomized?	Yes. See Figure 1. The primary analysis was an intention to treat analysis. A per protocol analysis excluding the cross over patients was not completed though they were few (PF/AJ N=1, EMS N=9)
Was the trial stopped early	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

PRIMARY OUTCOME: TREATMENT FAILURE

	TREATMENT FAILURE		
APPLE JUICE/PREFERRED FLUID (AJ/PF)	54	269	323
ELECTROLYTE MAINTENANCE SOLUTION (EMS)	81	243	324
	135	512	647

Prevalence: 135/647 = 20.8%
Absolute Risk (AJ/PF) = 54/323 = 16.7%
Absolute Risk (EMS) = 81/324 = 25%
Absolute Risk Difference = AR (AJ/PF) – AR (EMS) = 16.7% - 25% = - 8.3%, 95% CI (–∞ to -2%)

When each component of the composite outcome of treatment failure were analyzed separately, only the need for intravenous hydration was statistically significantly higher in the EMS than the AJ/PF group. The greatest difference was seen in those 54-60 months old.

Secondary Outcomes: Only intravenous rehydration at the initial ED visit was statistically significantly higher in the EMS group compared to the AJ/PF group. No adverse events were recorded

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The 1 sided 97.5% confidence interval for the absolute risk difference of 8.3% was –∞ to -2%. This is a statistically significant difference: the confidence interval does not include 0 and the p value is < 0.001. In the sample size determination, the authors considered AJ/PF non-inferior to EMS if it was not more than +7.5% worse than EMS. The upper limit of the confidence interval (-2%) meets the authors criteria for a clinically significant difference. When analyzed for superiority, the difference remained statistically significant as well.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. The demographic data from Table 1 seems similar to our patient population, though ethnicity was not provided. Since this was a Canadian population the majority of patiently have health insurance and a primary care provider.
Were all patient important outcomes considered?	No. The total volume of fluid intake was not provided for each group though the number of episodes of diarrhea and vomiting were equivalent. Hyponatremia was not assessed on all patients though none had symptomatic hyponatremia. Parental compliance with discharge instructions was not assessed.
Are the likely treatment benefits worth the potential harm and costs?	This is always a difficulty question. From a cost standpoint apple and preferred fluids would be cheaper than an electrolyte maintenance solution. The NNT is a quantitative measure of benefit. NNT = 1/ARD = 1/0.083 = 12. For every 12 patients treated with AJ/PF 1 additional patient would not have a treatment failure compared to EMS. No adverse events were seen to calculate a number needed to harm

CLINICAL BOTTOM LINE

BACKGROUND: Electrolyte maintenance (EMS) solutions are recommended for the treatment of dehydration by the World Health organization and the American Academy of Pediatrics. Oral rehydration recommendations are primarily based on studies from low/middle income studies and their applicability to high resource population and those with mild dehydration is unknown.

The potential benefits of a juice and preferred fluid regimen include a higher caloric intake than oral electrolyte solutions and a higher volume of fluids ingested. This should be balance with the potential for hyponatremia with hypotonic solutions and the potential for osmotic diarrhea with higher glucose concentrations. The electrolyte maintenance solution used in the study was apple flavored and sucralose sweetened to avoid palatability issues.

CLINICAL QUESTION: In pediatric patients with mild dehydration due to acute gastroenteritis is a regimen of ½ strength apple juice in the emergency department followed by preferred fluids (AL/PF) at home non-inferior to an electrolyte maintenance solution (EMS) in both settings in reducing treatment failures?

DESIGN/VALIDITY: This was a well design randomized clinical trial conducted at a single children's hospital and included 647 patients in the primary analysis. It is somewhat difficult to reconcile that almost 70% of the patients in the study were not considered dehydrated by the dehydration score with the overall 20% rate of treatment failure. There were no major risks of bias in the study's methodology. It may have been helpful to include a per protocol analysis accounting for crossover patients thought there were few of these (n=11). Compliance with discharge instructions was not assessed. The total volume of fluid ingested and the specific formulation of the EMS was not provided.

PRIMARY RESULTS: In the non-inferiority analysis the was a statistically significant reduction in treatment failure with apple juice/preferred fluids (ARD = AR (AJ/PF) – AR (EMS) = 16.7% - 25% = -8.3% 1 sided 97.5% confidence interval of –∞ to -2%). This difference was considered clinically significant by the authors criteria for non-inferiority of AJ/PF not more than +7.5% worse than EMS. When analyzed for superiority, there was difference statistically significant with AJ/PF superior to EMS. The greatest effect was found in those 54-60 months of age (ARD = -30.2%, 95% CO (-46, -8.2).

When each component of the composite outcome of treatment failure were analyzed separately, only the need for IV hydration (AJ/PF = 2.5%, EMS 9.0%, ARD = -6.5%, 95% CI(-11.6, -1.8) was statistically significantly higher in the EMS group than the AJ/PF group though it is unclear if this difference is clinically significant. A subgroup analysis of those with vomiting only compared to those with vomiting and diarrhea or diarrhea only may have been helpful. A subgroup analysis stratified by degree of dehydration also would have been helpful.

It is important to acknowledge that the study intervention was a composite of diluted apple juice in the emergency department and preferred fluids after discharge. It is not possible to assess the individual contribution of each of these interventions. It is unclear if both components were effective or if there may be a synergistic effect.

AUTHORS CONCLUSIONS: “Among children with mild gastroenteritis and minimal dehydration, initial oral hydration with dilute apple juice followed by their preferred fluids, compared with electrolyte maintenance solution, resulted in fewer treatment failures. In many high-income countries, the use of dilute apple juice and preferred fluids may be an appropriate alternative to electrolyte maintenance solution use in children with mild gastroenteritis and minimal dehydration.”

POTENTIAL IMPACT: The results of this study are encouraging and would greatly simplify parental management of gastroenteritis and mild dehydration at home. The authors acknowledge that the results may not be generalizable to low-middle income countries, other glucose electrolyte solutions and patients with higher degrees of dehydration.

GASTROENTERITIS:
DEHYDRATION RULE DERIVATION

In children 1 month to 5 years of age presenting to the emergency department with vomiting, diarrhea or poor oral fluid intake, do clinical parameters (history and physical examination) accurately predict the degree of dehydration as assessed by weight gain following resolution of illness?

Michael Mojica, M.D.
June 2017

Gorelick MH, Shaw KN, Murphy KO.

VALIDITY AND RELIABILITY OF CLINICAL SIGNS
IN THE DIAGNOSIS OF DEHYDRATION IN CHILDREN

Pediatrics. 1997 May; 99(5): E6.
PubMed ID: 9113963

STUDY DEFINITIONS	
POPULATION	Inclusion: 1 month to 5 years, complaint of vomiting, diarrhea, or poor fluid intake. Both patients discharged from the ED and those admitted were included. Exclusion: Symptoms > 5 days, history of cardiac or renal disease or diabetes mellitus, malnutrition or failure to thrive, hyponatremia or hypernatremia, treatment in prior 12 hours at another facility, tonsillectomy in prior 10 days, families without access to a telephone or beeper for follow-up. Setting: Single Children's Hospital ED, 1/1994-5/1995
INTERVENTION	Clinical Assessment: 10 signs of dehydration, 8 from World Health Organization assessment scale with the addition of heart rate and capillary refill. Performed by pediatric nurses and physicians with a minimum of 4 years' experience prior to the administration of oral or intravenous fluids. Categorical variables were classified as: normal, moderately abnormal, or markedly abnormal (later dichotomized to normal and abnormal) Treatment for dehydration was at the discretion of ED and inpatient providers Clinical Assessment Variables: *World Health Organization Variables General appearance* Quality of radial pulse* Quality of respirations* Skin Elasticity* Eyes* Tears* Mucous membranes* Urine output (by parental report)* Heart Rate Capillary refill (mean 3 finger readings)
CONTROL	Fluid Deficit: Based on weight gain following resolution of illness. Calculated as the percentage difference between initial and final weights. Clinically important dehydration defined as a fluid deficit of ≥ 5%. Weighed using a standard protocol: infants wearing only dry diaper, older children in a hospital gown without shoes. Admitted Patients: Weighed twice daily until discharge, using electronic scales in agreement with ED scales within 6.5%. Stable weight reached when two consecutive measurements differed by < 2%. Final weight was mean of last 2. Discharged Patients: (random 30% sample): Weighed at the end of the ED visit, and again at a scheduled follow-up visit at 48-72 hours. If follow up weights differed by > 2%, subsequent daily visits scheduled until stable weight achieved. Validation: Assessment of pre-illness weight from primary care provider data.
OUTCOME	Categorical Variables: Test characteristics dichotomized by combining "moderately abnormal" and "markedly abnormal" compared to "normal". Continuous Variables: Dichotomous test characteristics based on optimal cutoff on receiver operating characteristic curves
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. The clinical characteristic most commonly associated with dehydration were included.
Were all important predictors present in significant proportion of the study population?	Unclear. The proportions of patients with each predictor are presented in Table 2. Decreased skin elasticity (14%), capillary refill > 2 seconds (19%) and abnormal respirations (20%) were the least frequent predictors.
Were the outcome event and predictors clearly defined?	Yes. The outcome of fluid deficit was based on weight gain following resolution of illness. This was calculated as the percentage difference between initial and final weights. Clinically important dehydration defined as a fluid deficit of ≥ 5%. The 8 categorical predictors were initially assessed as normal, moderately abnormal, or markedly abnormal with descriptions for each category. Some of the descriptors are subjective. For example, sunken eyes versus very sunken eyes. A standardized approach to assessing capillary refill was utilized. It is unclear if heart rate was corrected for the presence of fever.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Yes. Those assessing the dehydration predictors were temporally blinded to the future outcomes of fluid deficit and those assessing the outcome were blinded to the predictors.
Was the sample size adequate (including an adequate number of outcome events)?	Likely yes. In general, 10 outcomes are required for each variable included in a rule derived by logistic regression. Since there are 4 predictors, the study would have required 40 patients with > 5% dehydration. Sixty-three children had dehydration, defined as a deficit of 5% or more of body weight.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

N = 186 (109 Inpatients, 77 Outpatients)
Median age: 13 months (89% < 36 months), 55% male
Dehydration: 63/186 (34%) > 5%, 11/186 (5.9%) > 10%

Test Characteristics (Table 2)
Average Sensitivity: 56%, range 35-85%.
Average Specificity: 84%, range 50-97%.
Heart rate: ROC curve optimal cutoff > 150 beats/min
Cap refill: ROC curve optimal cutoff > 2 seconds

	SENSITIVITY	SPECIFICITY
Decreased skin elasticity	35%	97%
Capillary refill < 2 seconds	48%	96%
Dry mucous membrane	80%	78%
Decreased urine output	85%	53%

LOGISTIC REGRESSION: 4 INDEPENDENT PREDICTORS	
PREDICTOR	ADJUSTED ODDS RATIO (95% CI)
Capillary Refill > 2 seconds	13.3 (3.4, 5.1)
Dry Mucous Membranes	4.3 (1.5, 12.6)
Absent Tears	4.3 (1.5, 12.4)
Abnormal General Appearance	3.0 (1.0, 8.8)

Rule Characteristics: 10 Predictor and 4 Predictor Rules
(See table in Clinical Bottom Line)
10 predictor rule: Area under the ROC curve = 0.9
4 predictor rule: Area under the ROC curve = 0.91
No statistically significant difference between the rules

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

Unclear. The rule does not specify a course of action such as those at high degree of dehydration require oral or intravenous hydration. However, attempts at rehydration could be limited to those assessed as has having dehydration possibly decreasing the length of ED stay and need for follow up for those without dehydration.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

No. There was not an internal validation cohort of the study results.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied?	☐ I ☐ II ☐ III ■ IV This is a level IV clinical decision rule. A level IV rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. The authors attempted to validate the reference standard by obtain pre-illness weight from the primary care providers but did not validate the rule. A level IV rule requires further validation before it can be applied clinically.
Does the rule make clinical sense?	Yes. The predictors in the rule are those factors that are typically considered when clinically assessing dehydration.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. Inter-rater reliability (kappa statistic) for 9 of the predictors based on 84 patients with two assessments are presented in Table 2. Inter-rater reliability was not assessed for heart rate. The average kappa was 0.6 with a range of 0.4-0.75. The predictors with the highest kappa were absent tears and decreased urine output (both 0.75). The predictors with the lowest kappa were abnormal respiration (0.4) and sunken eye (0.5). The kappa statistic for the 4 independent predictors from the regression analysis ranged from 0.59-0.75 (mean 0.65). The kappa for agreement for any 3 predictors was 0.68.
Is the rule applicable to the patients in my practice?	Likely. The setting was a single, urban pediatric ED. Only age and gender were provided for comparison to our population.
Will the rule results change my management strategy?	Use of the 4 predictor rule would simplify assessment of dehydration.
What are the benefits of applying the rule to my patients?	The primary benefit of applying the rule(s) is to identify those who are dehydrated and require rehydration before the dehydration progresses and require more invasive treatment such as intravenous hydration and admission to the hospital. In addition, patients without dehydration could forego hydration that is not necessary and be more rapidly discharged.
What are the risks of applying the rule to my patients?	As with any rule there is a potential for misclassification. Those with dehydration could be missed and those without dehydration could receive unnecessary treatment.

CLINICAL BOTTOM LINE

BACKGROUND: Studies of therapy for dehydration have been hampered by the lack of a clear gold standard to assess total body water. The diagnosis of dehydration is made primarily on clinical grounds. A documented recent weight loss is the most reliable sign of dehydration. In the absence of a prior weight, tachycardia is the most sensitive finding. No single sign is both sensitive and specific. Studies have demonstrated that physicians tend to clinically overestimate the degree of dehydration based on existing scale. One study found that 75% of admitted patients were less than 5% dehydrated.

CLINICAL QUESTION: In children 1 month to 5 years of age presenting to the emergency department with vomiting, diarrhea or poor oral fluid intake, do clinical parameters (history and physical examination) accurately predict the degree of dehydration as assessed by weight gain following resolution of illness?

DESIGN/RISK OF BIAS: This was a well-designed prospective cohort study to assess the accuracy of clinical findings in identifying dehydration. 186 patients were included in the primary analysis. 60 (32%) of which had dehydration of > 5%. 8 findings included in the World Health Association dehydration scale were assessed with the addition of heart rate and capillary refill. Nurses with more than 4 years of experience performed the assessments. Clear definitions were utilized though it is unclear if heart rate was corrected for fever and the heart rate cutoff of 150 beats/minute was not age specific.

Dehydration was defined as the change in weight at presentation compared to a stable weight at symptom resolution. An attempt was made to validate the outcome by obtaining pre-illness weights (n=19) from the patient's primary care provider. There was a near perfect correlation between pre-illness weight and post-illness weight, with correlation coefficient of 0.99.

It would have been helpful, at least for the inpatients, to present the amount of fluid received compared to ongoing fluid losses. In addition, it would have been helpful to repeat the clinical assessment at the time of symptom resolution to determine if the predictors had normalized.

PRIMARY RESULTS: All 10 predictors had a statistically significant association with dehydration. There was a direct relationship between number of predictors and the degree of dehydration. However, none of the 10 individual predictors had both a high sensitivity and specificity. The logistic regression analysis identified 4 of the 10 predictors (indicated in red in the table below) that were independent predictors of dehydration. The 4 predictor rule (area under the ROC curve = 0.91) performed similarly to the 10 predictor rule (area under the ROC curve = 0.90).

One of the problems with a composite rule that is based on the number or predictors present is that it assumes that each predictor has equal weight. This was not the case. In the regression analysis, the adjusted odds ratio for capillary refill > 2 seconds was over three times larger than the odds ratio for the closest of the other 3 predictors.

CLINICAL FINDINGS OF DEHYDRATION			
SIGNS AND SYMPTOMS	NONE OR MILD (0-5%)	MODERATELY ABNORMAL[1] (5-10%)	MARKEDLY ABNORMAL[1] (> 10%)
General Appearance: Infants[2]	Thirsty, alert restless	Lethargic or drowsy	Limp, cold, cyanotic extremities, coma
General Appearance: Older Children[2]	Thirsty, alert restless	Alert, postural dizziness	Apprehensive, cold, cyanotic extremities, muscle cramps
Quality of Radial Pulse	Normal	Thready or weak	Feeble or impalpable
Quality of Respiration	Normal	Deep	Deep and rapid
Skin Elasticity	Pinch retracts immediately	Pinch retracts slowly	Pinch retracts Very slowly (> 2 sec)
Eyes	Normal	Sunken	Very Sunken
Tears[2]	Normal	Absent	Absent
Mucous Membranes[2]	Moist	Dry	Very Dry
Urine output (parent report)	Normal	Reduced	None in many hours
Capillary Refill	≤ 2 seconds	> 2 seconds	NA
Heart Rate	≤ 150 beats/minute	> 150 beats/minute	NA
[1] Moderate Abnormal and Markedly Abnormal were combined into a single category of Abnormal			
[2] Independent predictors of dehydration in the Logistic Regression analysis			

RULE CHARACTERISTICS			
% DEHYDRATION	# RULE PREDICTORS	SENSITIVITY*	SPECIFICITY*
≥ 5%	≥ 3/10	87%	82%
≥ 10%	≥ 7/10	82%	90%
≥ 5%	≥ 2/4	79%	87%
≥ 10%	≥ 3/4	82%	83%
*Confidence intervals not provided			

The impact of the use of the rules on resource utilization is unclear. The rule does not specify a course of action such as those at high risk of dehydration require oral or intravenous hydration.

APPLICABILITY: The setting of the study was a single, urban children's hospital emergency department that included both patients that were managed in the ED and discharged and those requiring admission. It is likely the study's results are generalizable to similar settings. However, little demographic information on the study population is provided other than their age, gender and degree of dehydration. In addition, the study included only 11/186 (5.9%) with greater than 10% dehydration potentially limiting the applicability to those with severe dehydration.

The inter-rater reliability for 9 of the predictors was moderate to good (average kappa was 0.6 with a range of 0.4-0.75). Inter-rater reliability was not assessed for heart rate. The kappa statistic for the 4 independent predictors from the regression analysis ranged from 0.59-0.75 (mean 0.65). The kappa for agreement for any 3 factors was 0.68. The study assessors were highly trained pediatric nurses and physicians. Reliability may be lower with less experienced providers.

This is a level IV clinical decision rule. A level IV rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. The authors attempted to validate the outcome measure by obtain pre-illness weight from the primary care providers but did not internally validate the rule. A level IV rule requires further validation before it can be applied clinically.

AUTHOR'S CONCLUSION: "We recommend that existing criteria for the diagnosis of dehydration in children be modified to reflect the fact that objective signs of dehydration are apparent with a fluid deficit of > 5%. Of the 10 findings studied, none is sufficiently accurate to be used in isolation. The presence of fewer than three signs corresponds with a deficit of < 5%, whereas children with a deficit of 5% to 9% generally have three or more clinical findings. At least six to seven findings should be present to diagnose a deficit of 10% or more, although this recommendation is based on a limited number of subjects. It may be possible to rely on a relatively restricted subset of clinical indicators - general appearance, capillary refill, mucous membranes, and tears. Of these four findings, the presence of any two indicates a deficit of 5% or more, and three or more findings indicates a deficit of at least 10%. We are now planning future studies to evaluate better those children with severe dehydration, and to develop a valid prediction rule for dehydration incorporating historical and physical examination variables."

POTENTIAL IMPACT: Both the 10-predictor rule and the 4-predictor rule performed equally. The 4 predictor rule had a slightly higher average kappa (0.65 versus 0.60) though it is unclear if this small difference is clinically relevant. The 4-predictor rule would be easier to remember and thus simpler to use.

The primary benefit of applying the rule(s) is to identify those who are dehydrated and require rehydration before the dehydration progresses and require more invasive treatment such as intravenous hydration and admission to the hospital. In addition, patients without dehydration could forego hydration that is not necessary and be more rapidly discharged. As with any rule there is a potential for misclassification. Those with dehydration could be missed and those without dehydration would receive unnecessary treatment.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

GASTROENTERITIS: INTRAVENOUS DEXTROSE

In children 6 months to 6 years of age that present to the emergency department with symptoms of acute gastroenteritis (AGE) and who require intravenous fluids for dehydration, does an initial intravenous bolus with 5% dextrose in normal saline (D5NS) when compared to initial bolus with normal saline (NS) reduce the rate of hospitalization and lead to a greater reduction in serum ketone levels?

Rebecca Burton, M.D., Debbie Levine, M.D.
October 2, 2012

Levy JA, Bachur RG, Monuteaux MC, Waltzman M.

INTRAVENOUS DEXTROSE FOR CHILDREN WITH GASTROENTERITIS AND DEHYDRATION: A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL.

Ann Emerg Med. 2013 Mar;61(3):281-8.
PubMed ID: 22959318

STUDY DEFINITIONS	
POPULATION	Inclusion: 6 months-6 years, symptoms of gastroenteritis, received intravenous fluids for dehydration Exclusion: history of chronic illness, disorder of glucose metabolism, symptoms > 7 days, received intravenous fluids in previous 12 hours, suspected comorbid condition e.g. pneumonia, urinary tract infection, appendicitis. If initial bedside glucose < 40 or > 200 mg/dl Setting: Single Children's Hospital ED. 11/2007-12/2010
INTERVENTION	Fluid bolus 20 ml/kg D5 Normal Saline over 45-60 minutes (D5NS)
CONTROL	Fluid bolus 20 ml/kg Normal Saline over 45-60 minutes (NS)
CO-INTERVENTION	Diagnostic studies, medications (including antiemetics), disposition decision, amount or type or oral of intravenous fluids after the 1-hour initial fluid bolus was at clinical care team discretion. Discharged patients had phone follow up at 2-5 days
OUTCOME	Primary Outcome: Proportion admitted Secondary Outcomes: Change in serum ketone concentration (initial serum ketone value minus the 1- and 2-hour values). Discharged patients: Unscheduled medical care
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. An independent statistician performed computerized randomization in blocks of 10.
Was randomization concealed?	Yes. Treatment group allocation details were concealed. One pharmacist made all bags of intravenous solution, which were opaque, in the hospital pharmacy. There does not seem to be a way to bias randomization.
Were patients in the study groups similar with respect to known prognostic factors?	For the most part yes. Patients in the study groups were similar with respect to age, triage heart rate, median dehydration score, general appearance score, and baseline glucose, bicarbonate, and BUN level. The intravenous dextrose group had slightly higher baseline ketone levels, and a greater percentage of patients with acidosis (bicarbonate < 20 mmol/L) at baseline. This could potentially underestimate the efficacy in the dextrose group.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	All ED providers, enrollment staff and caregivers were blinded to treatment assignment, and intravenous solution bags were opaque. The treating physician, nurse, and caregivers were also blinded to bedside glucose and ketone testing results unless the glucose level was < 40 mg/dL or > 200 mg/dL, at which point the patient was removed from the study protocol.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDY'S CONCLUSION?	
Was follow-up complete?	Yes. There was no loss to follow-up for the study's primary outcome measure, hospital admission, or for its main secondary outcome measure, change in serum ketone level at 1 and 2 hours post initial IV fluid bolus. There was also no loss to follow-up for its secondary outcomes of change in general appearance score, ability to tolerate oral fluids, amount of fluid taken by mouth, and ED length of stay. No. For the secondary outcome measures of need for unscheduled care following ED discharge, follow-up in the D5NS group was 88.5% (54/61) and in the NS group was 86.8% (46/53).
Were patients analyzed in the groups to which they were randomized?	Yes. All patients were analyzed via intention-to-treat analysis, including 5 patients who were found to have co-morbid diagnoses.
Was the trial stopped early?	No. Trial was not stopped early.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Patient Characteristics
188 patients enrolled (94 in each group), 40% admitted
123/188 (65%) with metabolic acidosis
158/188 (84%) received Ondansetron
Mean initial serum ketone: 3.2 mmol/L (normal ≤ 0.2)

Primary Outcome: Proportion of Patients Hospitalized
Absolute Risk D5NS: 35.1%
Absolute Risk: NS: 43.6%
Absolute Risk Difference: 8.6% (-5, 22%)
(The authors considered a 20% difference to be clinically significant in their sample size determination)

Primary Outcome: Proportion of Patients Hospitalized
(Subgroup of patients with metabolic acidosis)
Absolute Risk D5NS: 46%
Absolute Risk: NS: 53%
Absolute Risk Difference: 8.6% (-10, 25%)

Secondary Outcomes:

Change in Serum Ketone Level (Baseline to 1 hour)
Mean reduction D5NS: Δ 1.2 mmol/L
Mean reduction NS: Δ 0.1 mmol/L
Mean reduction difference: 1.1 mmol/L (0.4, 1.9 mmol/L)

Change in Serum Ketone Level (Baseline to 2 hours)
Mean reduction D5NS: Δ 1.9 mmol/L
Mean reduction NS: Δ 0.3 mmol/L
Mean reduction difference: 1.6 mmol/L (0.0, 2.3 mmol/L)

Need for Unscheduled Medical Care
Absolute Risk D5NS: 17%
Absolute Risk NS: 24%
Absolute Risk difference: 7% (95% CI -9%, 23%)

Need for Unscheduled Medical Care
(Subgroup of patients with metabolic acidosis)
Absolute Risk D5NS: 11%
Absolute Risk NS: 30%
Absolute Risk difference: 19% (95% CI -2% - 40%)

There were no adverse events in either group

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Except for the results for reduction in serum ketone level at 1 and 2 hours, the confidence interval were wide (inprecise).

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	The patients were recruited from a single large, metropolitan, pediatric Emergency Department. However, based on the basic prognostic factors considered in Table 1 and the admission rates observed in this study (39.3% of study patients admitted, 79% with a dehydration score ≥ 3, 72% acidotic at presentation, 99% with a BUN/Cr ratio > 20), the acuity level of the patients in this study appears to be higher than that of most of our patients with acute gastroenteritis.
Were all patient important outcomes considered?	The study authors were thorough in their consideration of clinically important outcomes.
Are the likely treatment benefits worth the potential harm and costs?	The study did not demonstrate a statistically significant decrease in hospitalization. It did demonstrate a statistically significant decrease in serum ketone level overtime; however, the clinical significance of this finding is uncertain. The was a 7% less return for unscheduled care in the D5NS group though this was not statistically significant. There were no adverse events reported during the study. However, several of the study patients in the normal saline group were found to be hypoglycemic at 1 hour following the NS bolus. Conversely, in the D5NS group the study demonstrated a risk of endogenous insulin induced hypoglycemia following an intravenous bolus with a dextrose containing solution if the patient does not continue to receive dextrose via IV or PO routes.

CLINICAL BOTTOM LINE

BACKGROUND: Though acute gastroenteritis (AGE) is a very common pediatric illness that presents to the ED, the optimal method of intravenous fluid replacement in affected infants and young children who are severely dehydrated or who fail oral rehydration therapy is unclear. There is retrospective case-control study as well as anecdotal evidence suggesting that dehydrated children with AGE who receive more intravenous dextrose have a quicker resolution of ketoacidosis, with consequent improvement in nausea, poor oral intake, and emesis. This is the suggested therapy for pregnant women with hyperemesis gravidarum. The goal of this study was to determine whether an initial bolus of an intravenous dextrose-containing solution (vs. normal saline) would, through its triggering of increased endogenous insulin secretion, facilitate more rapid resolution of ketoacidosis and clinical improvement, leading to decreased rates of hospitalization.

CLINICAL QUESTION: In children 6 months to 6 years of age that present to the emergency department with symptoms of acute gastroenteritis (AGE) and who require intravenous fluids for dehydration, does an initial intravenous bolus with 5% dextrose in normal saline (D5NS) when compared to initial bolus with normal saline (NS) reduce the rate of hospitalization and lead to a greater reduction in serum ketone levels?

DESIGN/VALIDITY: This was a well-designed randomized clinical trial with no major validity concerns. Fluids received after the initial bolus were at the discretion of the treating physician and there were no specific criteria for admission.

PRIMARY RESULTS: This study did not demonstrate a statistically significant decrease in hospitalization rate for the D5NS group compared to the NS group. (Absolute Risk of admission D5NS = 35.1%, Absolute Risk of admission NS = 43.6%, Absolute Risk Difference: 8.6%, 95% CI (-5, 22%). In addition, there was no statistically significant difference in unscheduled return visits.
Study did demonstrate a statistically significant decrease in serum ketone level over time. However, the clinical significance of this finding is unknown.

APPLICABILITY: Admission criteria was not pre-specified in this study and was at the discretion of the patient's clinical care team. However, this study presents the reasons for admission in Table 2. The only statistically significant difference was admission by family request (NS: 5.3%, D5NS 15.9%). In addition, this was a group with significant dehydration as evidence by the degree of metabolic acidosis and azotemia. Perhaps patients with a less severe illness severity but still requiring intravenous rehydration may derive some benefit from dextrose containing intravenous fluids.

AUTHOR'S CONCLUSION: "Among dehydrated children requiring intravenous rehydration, administration of a dextrose-containing fluid bolus appears to be safe and led to a greater reduction in serum ketone levels compared with a bolus of normal saline solution. This did not translate, however, into a clinically significant reduction in a need for hospitalization. Further studies are needed to determine the optimal fluid regimen for rapid intravenous hydration in children presenting with gastroenteritis, dehydration, and metabolic acidosis."

POTENTIAL IMPACT: This was a well-designed study that did not demonstrate a benefit in admission or unscheduled return visits in children with dehydration due to acute gastroenteritis. The results of this study do not change the current strategy of intravenous rehydration with normal saline.

GASTROENTERITIS: NASOGASTRIC REHYDRATION

In children 6 months–6 years with acute gastroenteritis and moderate dehydration, is rapid (4 hours) nasogastric rehydration in the ED equivalent to standard (24 hours) nasogastric rehydration as an inpatient in preventing further dehydration?

Rebecca Burton, M.D., Dennis Heon, M.D.
November 2011

Powell CV, Priestley SJ, Young S, Heine RG.

RANDOMIZED CLINICAL TRIAL OF
RAPID VERSUS 24-HOUR REHYDRATION FOR
CHILDREN WITH ACUTE GASTROENTERITIS

Pediatrics. 2011 Oct;128(4): e771-8.
PubMed ID: 21949149

STUDY DEFINITIONS	
POPULATION	Inclusion: Age 6 months-6 years, acute viral gastroenteritis (sudden onset of non-bloody diarrhea (2 loose stools per 24-hour period) for 7 days, with or without vomiting), moderate dehydration (defined as a dehydration score of 3–6 age, diarrhea for 7 days), residence in an area covered by the Hospital-in-the-Home service Exclusion: Blood in stools, absence of diarrhea (vomiting only), significant other morbidity, dehydration score of ≤ 2 (minor) or ≥ 7 (severe) Setting: 2 Pediatric teaching hospitals (Australia), Enrollment not presented
INTERVENTION	Rapid Nasogastric Rehydration (RNR): 100 mL/kg ORS over 4 hours (25 mL/kg/hour) via nasogastric tube in ED. Discharged. Re-assessed by nurse by phone of home visit on following day.
CONTROL	Standard Nasogastric Rehydration (SNR): Admission, estimated fluid deficit (5-7% of bodyweight) replaced with oral rehydration solution over 6 hours via nasogastric tube. 24-hour maintenance fluid administered over next 18 hours. Rate reflected volume of ongoing losses.
OUTCOME	Primary Outcome: Treatment failure > 2% weight loss at any study point Secondary Outcomes: Treatment failure: 1. Inability to tolerate the insertion of nasogastric tube 2. Frequent or persistent vomiting 3. Intravenous rehydration 4. Continued signs of moderate dehydration (> 3 clinical signs) 5. Need for nasogastric fluids beyond 24 hours (SNR only) 6. Impending circulatory collapse.
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. A randomization list was generated by a computer using blocks of 6. One member of the research team supervised randomization though he was not involved in the clinical care of study patients.
Was randomization concealed?	Yes. Treatment group allocation details were stored in the ED in sequentially numbered, opaque, sealed envelopes. Group allocation remained concealed until written parental consent was obtained
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Patients in the study groups were similar with respect to age, Flores score used to estimate severity of gastroenteritis at initial assessment, Gorelick dehydration score used at initial assessment and at the time of randomization, admission weight, temperature, heart rate, and respiratory rate. However, study authors did not address whether patients within the two study groups were similar with respect to duration of symptoms prior to presentation.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The medical providers and study investigators were not blinded to the study interventions. The study authors note that “because of the nature of the treatments, blinding of the interventions was not possible”. It is unlikely that the lack of blinding would influence the objective primary outcome of > 2% weight loss or many of the secondary outcomes.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	No. There was loss to follow-up of 6/119 (5%) in the rapid nasogastric rehydration group, and 15/109 (13.8%) in the standard nasogastric rehydration group.
Were patients analyzed in the groups to which they were randomized?	No. Initially, there were 132 children randomized to the rapid nasogastric rehydration group, but 13 were excluded from analysis due to missing data (n=5), protocol violation (n=3), other illness (n=4), withdrawn consent (n=1). The study authors included 119 patients in the primary analysis. Similarly, there were initially 122 children randomized to the standard nasogastric rehydration group, but 13 were excluded from analysis due to missing data (n=6), protocol violation (n=2), other illness (n=5). The study authors used a sample size of 109 patients in the primary analysis. However, repeating the analysis on an intention-to-treat basis (both assuming none of the excluded children had primary or secondary treatment failure and assuming all the excluded children had primary or secondary treatment failure), the results are not significantly different from those presented.
Was the trial stopped early?	Yes. 228 patients were included in the primary analysis. The sample size determination required 254 patients. The reason for ending recruitment early was not presented.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Primary Outcome: Primary Treatment Failure: > 2% weight loss from admission
Rapid Nasogastric Rehydration: 14/119 = 11.8%, 95% CI (6.0, 17.6%)
Standard Nasogastric Rehydration: 10/109 = 9.2%, 95% CI (3.7, 14.7%)
Risk Difference: RNR–SNR = 11.8–9.2 = 2.6%, 95% CI (-5.3,10.5%)
Relative Risk: RNR/SNR = 11.8/9.2 = 1.18, 95% CI (0.50, 2.48)
No significant difference at any study time point

Secondary Outcomes: Secondary Treatment Failure defined as any of the following
1. Inability to tolerate NG tube insertion
2. Frequent or persistent vomiting
3. Need for intravenous fluid rehydration
4. Continued moderate dehydration (> 3 on dehydration score)
5. Need for nasogastric fluids beyond 24 hours
6. Impending circulatory collapse

Initial Post-therapy (RNR: 4 hours, SNR: 6 hours)
Rapid Nasogastric Rehydration: 27/119 = 22.7%,
Standard Nasogastric Rehydration: 29/109 = 26.6%
Risk Difference: 3.9%, 95% CI (-7.2, 15.1%)
Relative Risk: 0.85, 95% CI (0.54, 1.34), p>0.05

At 24 hours (Includes failures at 4-6 hours as well)
Rapid Nasogastric Rehydration: 36/119 = 30.3%
Standard Nasogastric Rehydration: 47/109 = 43.1%
Risk Difference: 12.9%, 95% CI (0.4, 24.9%)
Relative Risk: 0.7, 95% CI (0.49 – 0.99), p<0.05

At 7 days (Includes failures at 4-6 hours and 24 hours as well)
Rapid Nasogastric Rehydration: 39/119 = 30.3%
Standard Nasogastric Rehydration: 48/109 = 44.0%
Risk Difference: 13.8%, 95% CI (1.3, 25.8%)
Relative Risk: 0.68, 95% CI (0.48 – 0.97. p<0.05

Admission: RNR 36/199 = 30
Failure due to vomiting: RNR: 6/119 = 5.0%, SNR: 3/109 = 2.75%
Time in health care: RNS 35.5 hours, SNR 37.4 hours

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See confidence intervals for absolute risk differences and relative risks above

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Patients were recruited from a large, metropolitan, pediatric emergency department. Basic prognostic factors considered in Table 1. The primary difference was that study participants were required to reside in an area covered by “Hospital-In-The-Home” service.
Were all patient important outcomes considered?	Study authors were thorough in their consideration of clinically important outcomes. Though a scoring system was used to describe the severity of diarrheal illness it may also have been helpful to know the duration of illness.
Are the likely treatment benefits worth the potential harm and costs?	RNR may be worth consideration in a moderately dehydrated child with viral acute gastroenteritis if there is an excellent follow-up plan in place (and if the child’s parents are reliable and understand return precautions. RNR in this setting would not only spare the child the risks of hospitalization (potential exposure to nosocomial pathogens, psychological stress, etc.), but would also hopefully diminish potential psychosocial stress on the child’s parents and family, while saving the considerable expense of inpatient hospitalization.

CLINICAL BOTTOM LINE

BACKGROUND: Oral Rehydration Therapy (ORT) with a glucose-electrolyte solution has dramatically reduced global mortality rates for young children with acute. The American Academy of Pediatrics (AAP) currently recommends rapid oral rehydration for the treatment of children with viral gastroenteritis and moderate dehydration. The use of rapid hydration intravenously or via a nasogastric tube has not been extensively studied.

CLINICAL QUESTION: In children 6 months–6 years with acute gastroenteritis and Moderate hydration is rapid (4 hours) nasogastric rehydration in the ED equivalent to standard (24 hours) nasogastric rehydration as an inpatient in preventing further dehydration?

DESIGN/VALIDITY: The study authors' objective was to compare the efficacy of their standard rehydration regimen over 24 hours as an inpatient to rapid (4 hours) nasogastric rehydration in the emergency department. This was a well-designed study which included 207 patients in the primary analysis. The major validity concern with this study was that authors were not able to recruit enough patients to adequately power their study to meet the criteria of their non-inferiority hypothesis.

PRIMARY RESULTS: The primary failure rate, defined as weight loss of > 2% from baseline at any time during admission, were similar for RNR and SNR (RNR: 11.8%, SNR: 9.2%, Absolute Risk Difference: RNR – SNR= 11.8–9.2 = 2.6, 95% (-5.3,10.5%) $p > 0.05$. The author's goal was to determine if rapid rehydration was non-inferior to standard rehydration. The study failed to demonstrate non-inferiority. The authors failed to obtain the sample size required by their sample size determination resulting in larger confidence intervals around the risk difference. Secondary treatment failure was less common in the RNR group than in the SNR group. RNR: 39/119 = 30.3% SNR: 48/109 = 44.0% Absolute Risk Difference: 13.8%, 95% CI (1.3, 25.8%) $p < 0.05$.

APPLICABILITY: These results may not be applicable to our patient population. These patients had adequate access to follow-up care. In addition, this study did not address the use of antiemetics (Ondansetron) which has become commonplace. The time in health care was approximately 35 hours in the rapid nasogastric rehydration group. This may not be possible in many ED's without a dedicated observation area and nurses.

AUTHOR'S CONCLUSION: "Rapid nasogastric rehydration should be considered as an alternative to standard nasogastric rehydration for children (6 –72 months of age) with moderate dehydration attributable to viral gastroenteritis. Close follow-up monitoring after discharge from the ED is mandatory, to detect ongoing gastrointestinal losses or worsening dehydration. For patients who were readmitted after 24 hours of rapid nasogastric rehydration, a second period of nasogastric rehydration usually was effective; intravenous rehydration was required for only a small number of patients. Antiemetic agents, such as ondansetron, have been used in the ED to improve the efficacy of oral or nasogastric rehydration. Additional clinical studies to assess the role of antiemetic medications as an adjunct to rapid nasogastric rehydration for young children are encouraged."

POTENTIAL IMPACT: Rapid nasogastric rehydration over 4 hours in the Emergency Department may be worth consideration in a moderately dehydrated child with viral AGE who is unable to tolerate oral rehydration therapy if follow-up is readily available and if the child's parents are reliable and understand return precautions. Utilization of RNR in this setting would not only spare the child the risks of hospitalization but would also hopefully diminish potential psychosocial stress on the child's parents and family, while saving the healthcare system the considerable expense of inpatient hospitalization.

GASTROENTERITIS:
ORAL ONDANSETRON

In children presenting with symptoms of acute gastroenteritis and mild to moderate dehydration, does a single oral dose of Ondansetron when compared to Placebo result in a decrease in vomiting?

Eric Weinberg, M.D., Deborah Levine, M.D.
May 2005

Freedman SB, Adler M, Seshadri R, Powell EC.

ORAL ONDANSETRON FOR GASTROENTERITIS IN A PEDIATRIC EMERGENCY DEPARTMENT.

N Engl J Med. 2006 Apr 20;354(16):1698-705.
PubMed ID: 16625009

STUDY DEFINITIONS	
POPULATION	Inclusion: 6 months-10 years, acute gastroenteritis (≥ 1 episode of non-bilious, non-bloody vomiting within four hours, ≥ 1 episode of diarrhea), mild-to-moderate dehydration (< 24 months score 10-17, ≥ 24 months score 8-15) Exclusion: < 8 kg, severe dehydration, underlying disease that could affect assessment of hydration (e.g. renal failure, hypoalbuminemia), prior abdominal surgery, hypersensitivity to Ondansetron Setting: Single Children's Hospital ED, 1/2004-4/2005
INTERVENTION	Ondansetron: 2 mg (8-15 kg), 4 mg (15-30 kg), 8 mg (>30 kg). Oral dissolving tables (ODT). A second dose was given if vomiting occurred within 15 minutes
CONTROL	Placebo of similar taste and appearance
CO-INTERVENTIONS	1 hour period of oral rehydration therapy initiated 15 post study drug. Maximum of 30 ml of an oral rehydration solution Q5 minutes
OUTCOME	Primary Outcome: Proportion vomited while receiving oral-rehydration therapy (Vomit defined as forceful expulsion of stomach contents, Episodes < 2 minutes apart considered as single episode) Secondary Outcomes: Number of episodes of vomiting during oral-rehydration therapy Rates of intravenous rehydration and hospitalization Diarrhea Phone follow-up: Day 3,7: Return visits, IV hydration, admission symptoms
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized in blocks of 6 to receive Ondansetron or Placebo.
Was randomization concealed?	Yes. A statistician provided code to pharmacy, then dispensed drug to the ED in opaque bags. Pills had similar color and taste.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. (Table 2) No statistically significant difference between the two groups for measured prognostic factors. Clinically, there were more patients in the Ondansetron group with a lower dehydration score of 9-10 (29 vs 24). However, this difference was balanced by the lesser number of Ondansetron patients with a score of 10-11 (51 vs 58), which is still considered mild dehydration.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Only the statistician and pharmacist knew of group allocation. The bedside nurse administered the medication while the research assistant was outside the room to ensure that the research assistant, physician, child, and caregivers remained unaware of the treatment assignment.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. There was 100% follow up for Ondansetron patients at day 3 and 98% at Day 7. Placebo group follow up was 96% at Day 3, 94% at Day 7.
Were patients analyzed in the groups to which they were randomized?	Yes (Figure 1). An intention to treat analysis was utilized, although not directly stated. The one patient that was not included in the analysis was randomized without parental consent and was subsequently removed.
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Primary Outcome: Vomiting during oral rehydration (within 1hour)
Absolute Risk Ondansetron: 15/107 = 14.1%
Absolute Risk Placebo: 37/107 = 34.5%
Absolute Risk Difference: 34.5% - 14.1% = 20.6%, 95% CI (9.1, 31.4%)
Relative Risk: 14%/35% = 0.40, 95% CI (0.26, 0.61)
(The authors considered a 20% absolute risk difference to be clinically significant)

Secondary Outcomes:

1. Vomiting episodes (#): Ondansetron 0.18 vs Placebo 0.65,
   Relative Risk: 0.30, 95% CI (0.18, 0.50)

2. Intravenous Hydration: Ondansetron 14% vs Placebo 31%,
   Relative Risk: 0.46, 95% CI (0.26-0.79)
   Risk Difference: 95% CI 16.8% (5.7, 27.5%)

4. Amount consumed: Ondansetron 239 ml vs Placebo 196 ml
   Mean Difference: 43 ml

5. Hospitalization: Ondansetron 4% vs Placebo 5%
   Relative Risk: 0.80, 95% CI (0.22, 2.9),
   Risk Difference: 0.9%, 95% CI (-5.2, 7.2%)

6. Diarrhea episodes: Ondansetron 1.4 vs Placebo 0.5
   Mean difference: 0.9 episodes

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

95% Confidence Intervals provided with relative risk above. All represent statistically significant difference with the exception of hospitalization due to the small number of events.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. Pediatric ED setting, age 6 months to 10 years with mild/moderate dehydration and symptoms of AGE. However, no mention of ethnicity of population. Cultural and language barriers may affect efficacy of oral rehydration regimen since it is parent-dependent.
Were all patient important outcomes considered?	Yes and No. They measured vomiting occurrence (yes vs no) during oral rehydration, # episodes vomiting, IV hydration (yes/no and ml of fluids given), ml of PO hydration, and length of stay in ED. They also measured several outcomes at follow up. There are two potential improvements with the study design. First would be to use a validated dehydration scale. A second improvement would be to use the WHO guidelines and measure oral rehydration over 4 hours, allowing for maximum effect of Ondansetron (peak onset of action occurs at 2 hours). The authors only measured oral rehydration for 1 hour, 15 minutes after Ondansetron was given. There might have been an even greater treatment effect if authors allowed more time for Ondansetron to take effect.
Are the likely treatment benefits worth the potential harm and costs?	Yes. The number needed to treat (NNT) for the primary outcome = 5. Need to treat 5 patients with Ondansetron to prevent 1 additional patient from vomiting during oral rehydration compared to placebo. NNT = 6 to prevent one child from receiving intravenous hydration. Authors calculated reduction of cost if intravenous hydration avoided = $4,145 in this study. However, in their analysis they did not figure in the cost of treating all acute gastroenteritis patients with Ondansetron. Potential harm is the adverse effect of diarrhea from Ondansetron. There were significantly more episodes of diarrhea with Ondansetron vs placebo (1.4 vs 0.5), although this difference is likely to not be clinically relevant. In addition, the increase in diarrhea may represent increased fluid taken in by the Ondansetron group.

CLINICAL BOTTOM LINE

BACKGROUND: Oral rehydration therapy is the primary method recommended for rehydration of the child with mild-moderate dehydration due to acute gastroenteritis. Oral rehydration may be limited by the child's refusal to take liquids or more commonly persistent vomiting. A safe and effective anti-emetic could improve the success of oral rehydration. Ondansetron is FDA approved in children for use in those who are post-operative and those receiving chemotherapy.

CLINICAL QUESTION: In children presenting with symptoms of acute gastroenteritis and mild to moderate dehydration, does a single oral dose of Ondansetron when compared to Placebo result in a decrease in vomiting?

DESIGN/VALIDITY: This is a well-designed randomized controlled trial to determine whether a single dose of ondansetron can decrease vomiting in children with acute gastroenteritis and mild/moderate dehydration who are undergoing oral rehydration therapy. The primary intention to treat analysis included 214 patients (107 in each treatment group). There were no major validity concern. The use of a validated dehydration scale and a study period of greater than 1 hour may have been useful.

PRIMARY RESULTS: A single dose of Ondansetron resulted in a clinically and statistically significant decrease in both the number of patients who vomited during oral rehydration therapy (Absolute risk Difference: 34.5%-14.1% = 20.6%, 95% CI (9.1, 31.4%)) and the mean number of vomiting episodes in the ED setting (Ondansetron 0.18 vs Placebo 0.65 RR 0.30, 95% CI (0.18-0.50)). Other potential benefits include a decrease in the requirement for intravenous rehydration and an increase in the volume or oral fluids tolerated in the hour after Ondansetron was administered. The authors found no difference in hospitalization rates, although this may have been limited by low number of total hospitalizations. The treatment effect may have been larger if more time was allowed for Ondansetron to take effect. Patients in the Ondansetron group had slightly more episodes of diarrhea, (0.9 episodes) although the difference found is unlikely to be clinically significant.

APPLICABILITY: The study results are likely generalizable to patients in the emergency department meeting study inclusion and exclusion criteria. However, the ethnicity of the study population was not presented. Cultural and language barriers may affect efficacy of oral rehydration regimen since it is parent-dependent. The number needed to treat for the primary outcome is 5 (NNT = 1/ARD = 1/0.2). Would need to treat 5 patients with Ondansetron to prevent 1 additional patient from vomiting during oral rehydration when compared to Placebo.

AUTHOR'S CONCLUSION: "We found that treatment with orally disintegrating ondansetron tablets was beneficial in children with vomiting and dehydration due to gastroenteritis. The ondansetron tablet is easy to administer, has few side effects, and is safe and effective. Therefore, it may be a useful therapy in the emergency department for children with vomiting and mild-to-moderate dehydration because of gastroenteritis."

POTENTIAL IMPACT: This is a well-designed study that demonstrated a clinically and statistically significant reduction in vomiting during oral rehydration for mild-moderate dehydration due to acute gastroenteritis with a small number need to treat. The benefit seen in the secondary outcomes and lack of adverse events add to the potential for Ondansetron as an adjunct to oral rehydration therapy

GASTROENTERITIS:
ORAL REHYDRATION THERAPY

In infants and children with moderate dehydration due to acute gastroenteritis in the emergency department, is oral rehydration therapy non-inferior to intravenous rehydration therapy in reducing dehydration and resolving symptoms at 4 hours after treatment initiation?

Ramona Warren, M.D., Michael Tunik, M.D.
April 2005

Spandorfer PR, Alessandrini EA, Joffe MD, Localio R, Shaw KN.

ORAL VERSUS INTRAVENOUS REHYDRATION OF MODERATELY DEHYDRATED CHILDREN: A RANDOMIZED, CONTROLLED TRIAL.

Pediatrics. 2005 Feb;115(2):295-301.
PubMed ID: 15687435

STUDY DEFINITIONS	
POPULATION	Inclusion: 8 weeks -3 years, moderately dehydrated (dehydration score 3-7, corresponding to 5–10% dehydration), probable viral gastroenteritis (3 loose or watery stools in the previous 24 hours), a parent or legal guardian available to remain with the patient, phone number for contact at 72 hours follow-up Exclusion: Hypotension (systolic blood pressure 2 SDs below the mean for age on 2 repeated measures), duration of illness 5 days, history of chronic illness that would influence fluid status (e.g., renal disease), malnutrition, failure to thrive, impaired oromotor skills, received treatment at any ED within 12 hours Setting: Observation area of a single Children's Hospital ED. 12/2001-4/2003.
INTERVENTION	Oral Rehydration Therapy (ORT): Pedialyte 50 mL/kg over 4 hours for dehydration score 3-5, Pedialyte 75 mL/kg over 4 hours for dehydration score 6 Divided into 5 ml aliquots. Administered by parents after instruction by trained nurses A sham intravenous catheter was placed
CONTROL	Intravenous Fluids (IVF): Two 20 mL/kg normal saline boluses within the 1st hour. After fluid bolus encouraged drink oral fluids during the next 3 hours. Pedialyte offered first, but if refused or parents requested, water or juice was allowed.
OUTCOME	Primary Outcome: Success of treatment in the ED at 4 hours (0 of the 4 criteria) 1. Resolution of moderate dehydration (4-hour dehydration score) 2. Weight gain 3. Production of urine output during the trial 4. Absence of severe emesis (5 mL/kg) during the fourth hour of the trial. Secondary Outcomes: 1. Time to initiate therapy 2. Improvement in the dehydration score after 2 hours 3. Hospitalization rate (disposition decision was unmasked 4. Parental therapy preference at 4 hours 5. 72-hour ED revisits
DESIGN	Interventional: Randomized clinical trial (Non-inferiority hypothesis)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized in blocks of 6, 8 and 10 using a random numbers table, and within the blocks also using a random numbers table.
Was randomization concealed?	Yes. Randomization was not revealed until the consent had been obtained and the patient ushered into the treatment room. The investigators did not appear to have the opportunity to bypass the randomization process.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Table 1 shows the baseline characteristics of the study population and there do not appear to be any clinically significant differences in the population. Comparison made between refusals and the study population revealed no significant differences in age, gender, or baseline dehydration score. Patients in the intravenous fluid group received more total fluids than patients in the oral rehydration group (61 versus 43 ml/kg) potentially biasing results in favor of intravenous rehydration.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	No, Clinicians were unaware of group allocation until the trial period was completed, including during the 2 and 4-hour reassessment periods (sham intravenous catheters were in place, patient removed to a different room than the treatment room). Treatment was revealed prior to final disposition of the patient (home versus admit). The nurse practitioner who administered the treatment was aware of the group allocation but was not involved in assessing outcomes. Patients and their parents were made aware of the group allocation when treatment was administered.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. All patients were accounted for in the analysis and none were lost to follow-up.
Were patients analyzed in the groups to which they were randomized?	Yes. This was an intention-to-treat analysis. They also performed an analysis based on treatment received with the minor differences in the results noted in the article.
Was the trial stopped early?	Yes. The trial intended to enroll 100 subjects. The trial was stopped early when enrollment declined in the second season as oral rehydration therapy was adopted and often initiated prior to study initiation.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

PRIMARY OUTCOMES

	ORT (36)	IVF (37)	RISK DIFFERENCE (95% CI)
Dehydration resolved	90.6%	82.9%	7.8% (-8.3, 23.8%)
Produced urine	88.2%	85.7%	2.5% (-13.3, 18.4%)
Weight gain	82.8%	100%	-17.2% (-31, -3.5)
No severe emesis	100%	100%	0%
OVERALL SUCCESS	55.6%	56.8%	- 1.2 (-24, 21.6%)

SECONDARY OUTCOMES

	ORT	IVF	RISK DIFFERENCE (95% CI)
Time to initiate Treatment	19.9 min	41.2 min	21.2% (10.3, 32.1)
Improved score 2 hours	78.8%	80%	-1.2% (-20.5,18)
Admit	30.6%	48.7%	-18.1% (-40.1, 4)
Parental preference	6.13%	51.4%,	9.9%(-14, 33.7)
72 hour ED revisit	9.1%	8.3%,	0.8%(-12.6, 141)

Fluid parameters (Table 4): The intravenous fluid group had a higher mean fluid intake and weight gain compared to the oral rehydration group. Urine output was the same
15.2%, 95% CI (2.7, 27.6%) in the ORT group required IV fluids.
49.6% of the IV fluids group required > 1 IV attempt

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The 95% confidence intervals for the risk differences are listed above. The small sample size results in wide (imprecise) confidence intervals. A non-inferiority margin was not presented.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. Inclusion/exclusion criteria and patient characteristics appear similar to our population. Patients we are most concerned about regarding dehydration status are the under 3 age group and this study focuses solely on that group. The racial mix and parent education seems slightly different. The study interventions took place in an ED observation area with dedicated nursing staff and may not be applicable to other settings to the main ED or other settings.
Were all patient important outcomes considered?	Yes. All clinically important outcomes appear to have been considered.
Are the likely treatment benefits worth the potential harm and costs?	There was slightly more vomiting in the ORT group during the study period however not in the last hour. There was no difference in improvement of dehydration and there was faster initiation of treatment even with experienced intravenous starters who had all of their equipment prepared. There were some failures (5) of oral rehydration requiring IV starts, but for the rest, the pain and anxiety of IV placement was avoided (although that should be compared that to the pain and anxiety of slightly more episodes of emesis (1.2% in ORT versus 0.4% in IVT).

CLINICAL BOTTOM LINE

BACKGROUND: Oral rehydration therapy is recommended by World Health Organization and the American Academy of Pediatrics as first-line therapy for mild to moderate dehydration. It is simple and inexpensive to administer and is a treatment that parents can perform at home. In the emergency department setting intravenous hydration is often the first line therapy.

CLINICAL QUESTION: In infants and children with moderate dehydration due to acute gastroenteritis in the emergency department, is oral rehydration therapy non-inferior to intravenous rehydration therapy in reducing dehydration and resolving symptoms at 4 hours after treatment initiation?

DESIGN/VALIDITY: This is a very well designed without major valid concerns. The study included 73 patients in the primary intention to treat analysis.

PRIMARY RESULTS: For the composite outcome of overall success, the two groups were nearly identical (ORT 55.6%, as IVF 56.8%, Absolute risk difference: 1.2% 95% CI (-24.0, 21.6%)). The authors concluded that “ORT is as good IVF” though the trial was stopped early and a non-inferiority margin was not presented. This is particularly important given the small sample size. The lower limit of the confidence interval for the risk difference is -24%. Oral rehydration therapy that is 24% worse than intravenous fluids would need to be considered acceptable to conclude that oral rehydration is non-inferior to intravenous fluids. 15.2% (2.7,27.6%) in the oral rehydration group ultimately required intravenous fluids.

APPLICABILITY: The study interventions took place in an ED observation area with dedicated nursing staff. In addition, oral rehydration therapy requires parental assistance. The study results may not be generalizable populations with limited English proficiency and to a main ED or non-ED settings.

AUTHOR’S CONCLUSION: “We demonstrated in this clinical trial that ORT is as good as IVF in rehydration of moderately dehydrated children due to gastroenteritis. In addition, we found that less time was required to initiate ORT when compared with IVF in the ED. In our treatment-received analysis, patients treated with ORT had fewer hospitalizations. The results of this study suggest that ORT be the initial treatment of choice for moderately dehydrated children 3 years old with gastroenteritis.”

POTENTIAL IMPACT: This study demonstrates the safety and efficacy of oral rehydration therapy in an emergency department setting when compared to intravenous therapy in an ED observation. The conclusion that oral rehydration is non-inferior to intravenous fluids may not be justified given the lower limit of the confidence interval for treatment success. The decrease in the pain associated with sometimes multiple attempts at IV placement and the ability of the parents to complete oral rehydration at home make oral rehydration an attractive initial option with intravenous fluids as a backup plan.

GASTROENTERITIS: PROBIOTICS

In children 3 months to 4 years of age with acute gastroenteritis does a 5 day course of Probiotics (Lactobacillus rhamnosus) when compared to Placebo result in a reduction in moderate to severe gastroenteritis within 14 days after enrollment?

Michael Mojica, MD
December 2018

Schnadower D, Tarr PI, Casper TC, Gorelick MH, Dean JM, O'Connell KJ, Mahajan P, Levine AC, Bhatt SR, Roskind CG, Powell EC, Rogers AJ, Vance C, Sapien RE, Olsen CS, Metheney M, Dickey VP, Hall-Moore C, Freedman SB.

LACTOBACILLUS RHAMNOSUS GG VERSUS PLACEBO FOR ACUTE GASTROENTERITIS IN CHILDREN.

N Engl J Med. 2018 Nov 22;379(21):2002-2014.
PubMed ID: 30462938

STUDY DEFINITIONS	
POPULATION	Inclusion: 3 months-4 years, acute gastroenteritis defined as ≥ 3 watery stools per day with/without vomiting for < 7 days Exclusion: Risk factors for bacteremia (immunocompromised, systemic corticosteroids within 6 months, indwelling catheter, structural heart disease, prematurity if less than 6 months) Chronic gastrointestinal disorders, pancreatitis, bilious emesis, hematochezia Allergy to L. rhamnosus, microcrystalline cellulose, erythromycin, clindamycin, beta-lactam antibiotics (in case treatment required for severe infection) Did not speak English or Spanish Setting: Multicenter (10) PECARN network emergency departments, 7/14-6/17
INTERVENTION	Probiotic: Lactobacillus rhamnosus ($1x10^{10}$ colony forming units) BID x 5 days
CONTROL	Placebo: Identical appearance
OUTCOME	Primary Outcome: Moderate to Severe gastroenteritis defined as a score ≥ 9 on the modified Vesikari score (range 0-20), See appendix Secondary Outcomes: 1. Duration and frequency of diarrhea and vomiting 2. Unscheduled health care visits within 2 weeks for gastroenteritis symptoms 3. Days of daycare missed 4. Hours of caregiver absence from work 5. Rate of household transmission: Development of gastroenteritis in previously asymptomatic household contacts 6. Safety: L. rhamnosus Extra-intestinal infection, side effects, adverse events
	Caregivers completed a daily diary Follow up data obtained by phone or email daily x 5 days, 14 days and 1 month Predefined subgroups: Age (< 1year, ≥ 1 year), duration of symptoms (< 48 hours, ≥ 38 hours), antibiotic use in the past 14 days, pathogen (viral, bacterial, none detected)
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. A web-based system was used to randomize patients in permuted blocks. Groups were stratified by trial site and duration of symptoms (< 48 hours, ≥ 48 hours)
Was randomization concealed?	Unclear. It is not explicitly stated that randomization was concealed but the probiotic and placebo were identical in appearance, texture and taste and it does not appear to be an opportunity to bias allocation
Were patients in the study groups similar with respect to known prognostic factors?	Yes. (Table 2). Patients were similar with regard to demographic characteristics, disease severity (categories of the modified Vesikari score), degree of dehydration, pathogens identified and additional treatments (antibiotics, Zofran).
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Care givers, physicians and those assessing the trial outcomes were blinded to group allocation.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. (Figure 1). 971 patients were randomized. 3.1% (15/483) were lost to follow up in the Probiotic group. 2.7% (13/488) were lost to follow up in the Placebo group
Were patients analyzed in the groups to which they were randomized?	Yes. The primary outcome was analyzed as an intention to treat population (Figure 1). A per protocol analysis was also completed and the results were similar to the intention to treat population.
Was the trial stopped early?	No. A data safety and monitoring board reviewed the trial at multiple time intervals. The sample size determination identified 670 participants. The number was increased to 970 to account for those lost to follow up. 943 patients were included in the primary analysis.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N=943 (Probiotic: 468, Placebo: 475)
Median age: 1.4 years, IQR (0.9, 2.3),
82% with moderate-severe disease at presentation (5% admitted)
Compliance (≥ 7/10 doses): Probiotic: 86.5%, Placebo 87.8%

Primary Outcome: Moderate-Severe gastroenteritis (Modified Vesikari score ≥ 9)

	Moderate-Severe AGE		
	YES	NO	
Probiotic	55	413	468
Placebo	60	415	475
TOTAL	115	828	943

Probiotic group: 11.8% (55/468)
Placebo group: 12.6% (60/475)
Risk Difference: 0.9%, 95% CI (-3.3, 5.1%)
Relative Risk: 0.96, 95% CI (0.68, 1.35)
The authors considered a 10% difference in the primary outcome to be clinically significant

There was no difference in the analysis of the individual components of the modified Vesikari score
There was no difference between the intention to treat and per protocol analysis
There was no difference in the primary outcomes in the subgroups based on: age, duration of symptoms, antibiotic use or pathogen identified

SECONDARY OUTCOMES (TABLE 3)

	Diarrhea	Vomiting	Admit	IV Fluids	Absent	Revisit	Transmission
Probiotic group	49.7 hours	0 hours	3.2%	4.1%	2 days	12.2%	10.6%
Placebo group	50.9 hours	0 hours	3.2%	4.6%	2 days	16.8%	14.1%

Adverse events
Extra-intestinal L rhamnosus infections: 0,
Rates of adverse events: No difference except wheezing: Probiotic: 1.1% (5), Placebo 0.0% (0)
Rates of side effects: No difference

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The 95% confidence interval for the Risk Difference: 0.9%, 95% CI (-3.3, 5.1%) and Relative Risk: 0.96, 95% CI (0.68, 1.35) were fairly narrow.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. The study was conducted in 10 pediatric children's hospital Emergency Department making the study's results generalizable to those meeting inclusion an exclusion criteria in that setting.
Were all patient important outcomes considered?	Yes. The primary outcome consists of multiple measures of disease severity. In addition, outcomes of concern to parents such as daycare absenteeism and days lost from work were included.
Are the likely treatment benefits worth the potential harm and costs?	There were neither benefits or harms associated with probiotics.

CLINICAL BOTTOM LINE

BACKGROUND: Acute gastroenteritis is the second leading cause of death in children worldwide. While death from gastroenteritis is rare in the US, it leads to a high number or emergency department visits and hospital admissions. It is also associated with loss of time from work for parents and a risk of transmission to other contacts. The primary management of acute gastroenteritis is the maintenance of hydration. Meta-analyses have revealed a potential benefit of probiotics though the included trials suffer from methodologic limitations.

CLINICAL QUESTION: In children 3 months to 4 years of age with acute gastroenteritis does a 5 day course of probiotics (Lactobacillus rhamnosus) when compared to Placebo result in a reduction in moderate to severe gastroenteritis within 14 days after enrollment?

DESIGN/VALIDITY: This was a well-designed, randomized, blinded, placebo controlled randomized clinical trial including 943 in the primary intention to treat analysis of pediatric patients with acute gastroenteritis at 10 pediatric children's hospital emergency departments in the PECARN network. Patients were randomized to Probiotic (Lactobacillus rhamnosus: 1x1010 colony forming units BID x 5 days) or an identical Placebo. The primary outcome was the proportion of patients with moderate-severe disease based on the a score ≥ 9 on the modified Vesikari score. Secondary outcomes included: the duration and frequency of diarrhea and vomiting, unscheduled health care visits within 2 weeks for gastroenteritis symptoms, days of day care absenteeism, hours of caregiver absence from work, the rate of household transmission, L. rhamnosus extra-intestinal infection, side effects and adverse events. iHealth provided the probiotic and placebo capsules but was not involved in the trial in any other way. An analysis of the probiotic capsules revealed that in some capsules (n=36) the dose was lower than intended. A sensitivity analysis of the primary and secondary outcomes were similar when the patients who received the incorrect dose were excluded.

PRIMARY RESULTS: 943 patients (Probiotic: 468, Placebo: 475) were included in the primary analysis. The median age was 1.4 years, IQR (0.9, 2.3). Compliance (receiving ≥ 7/10 of the intended doses was 86.5% in the Probiotic group and 87.8% in the Placebo group.

There was no difference in the primary outcome of moderate-severe gastroenteritis between the two treatment groups (Probiotic group: 11.8%, Placebo group: 12.6%,, Risk Difference: 0.9%, 95% CI (-3.3, 5.1%)). The authors considered a 10% difference to be clinically significant. There was no difference in the analysis of the individual components of the modified Vesikari score. There was no difference in the per protocol analysis and no difference in the subgroup analysis base on age duration of symptoms, antibiotic use or pathogen identified.

There was no difference in the secondary outcomes of: the duration and frequency of diarrhea and vomiting, unscheduled health care visits within 2 weeks for gastroenteritis symptoms, days of daycare absenteeism, hours of caregiver absence from work, the rate of household transmission. There were no cases of L. rhamnosus extra-intestinal infection. There was no difference in adverse effects with the exception that 1.1% of Probiotic group had wheezing compared to 0% in the Placebo group.

APPLICABILITY: The study was conducted in 10 pediatric children's hospital Emergency Departments making the study's results generalizable to those meeting inclusion an exclusion criteria in that setting. Applicability to other settings, other probiotic organisms and other countries is unclear.

AUTHOR'S CONCLUSION: "In this randomized, placebo-controlled trial involving 971 preschool children with acute gas- troenteritis,thosewhoreceiveda5-daycourseof L. rhamnosus GG did not have better outcomes than those who received placebo. Treatment with L. rhamnosus GG did not result in a smaller proportion of participants having moderate-to-severe gastroenteritis and failed to show benefit with respect to the duration or frequency of vomiting or diarrhea, the rate of household transmission, or the duration of day-care or work absenteeism."

POTENTIAL IMPACT: This well-designed large, multicenter randomized, placebo controlled trial of probiotics in children with acute gastroenteritis did not find a benefit in any of the primary or secondary outcomes measures or in any of the subgroup analyses. Probiotics cannot be recommended based on this trial

APPENDIX: MODIFIED VESIKARI SCORE				
	0	1	2	3
Diarrhea duration (hours)	0	1-96	97-120	≥ 121
Max # watery stools/24h	0	1-3	4-5	≥ 6
Vomiting duration (hours)	0	1-24	25-48	≥ 49
Max # vomiting/24 hours	0	1	2-4	≥ 5
Max Recorded Temp (C)	< 37.0 C	37.1-38.4 C	38.5-38.9CC	≥ 39.0 C
Unscheduled healthcare	0	NA	Primary Care	ED
Treatment	None	IV Hydration	Admission	NA

Schnadower D, Tarr PI, Gorelick MH, O'Connell K, Roskind CG, Powell EC, Rao J, Bhatt S, Freedman
Validation of the modified Vesikari score in children with gastroenteritis in 5US emergency departments.
J Pediatr Gastroenterol Nutr. 2013 Oct;57(4):514-9., PubMed ID: 23676445

See also:

Freedman SB, Williamson-Urquhart S, Farion KJ, Gouin S, Willan AR, Poonai N, Hurley K, Sherman PM, Finkelstein Y, Lee BE, Pang XL, Chui L, Schnadower D, Xie J, Gorelick M, Schuh S; PERC PROGUT Trial Group.
Multicenter Trial of a Combination Probiotic for Children with Gastroenteritis
N Engl J Med. 2018 Nov 22;379(21):2015-2026., PubMed ID: 30462939

GENITOURINARY & RENAL

1. AKI: Contrast CT: Meta-analysis: Annals EM 2018
2. Renal Stones: POCUS Hydronephrosis: Annals EM 2014
3. Scrotal Pain: Torsion Decision Rule: J Urol. 2013
4. UTI: Adverse Event Rule Derivation: Pediatrics 2010
5. UTI: Decision Rule Derivation: Arch Ped Adol Med. 2000
6. UTI: Derivation of a UTI Risk Calculator: JAMA Peds 2018
7. UTI: Disposition and Revisits: Academic Pediatrics 2019
8. UTI: Outpatient Management: Pediatrics 1999

ACUTE KIDNEY INJURY: CONTRAST NEPHROPATHY

In adult patients undergoing CT with intravenous contrast when compared to CT without intravenous contrast, what is the risk of acute kidney injury defined as a relative or absolute increase in serum creatinine?

Michael Mojica, MD
February 2019

Aycock RD, Westafer LM, Boxen JL, Majlesi N, Schoenfeld EM, Bannuru RR.

ACUTE KIDNEY INJURY AFTER COMPUTED TOMOGRAPHY: A META-ANALYSIS.

Ann Emerg Med. 2018 Jan;71(1):44-53.e4.
PubMed ID: 28811122

STUDY DEFINITIONS	
POPULATION	Inclusion: Non-interventional studies, adults, comparing the incidence of renal insufficiency after contrast CT compared to non-contrast CT Exclusion: Pediatric studies, intra-arterial procedure studies, prevention strategy studies, case reports, review articles, clinical guidelines, meta-analyses Setting: Countries of included studies not presented. Included ED, ICU, inpatient and mixed settings, Search included studies prior to 12/2016
EXPOSURE	Any CT with Intravenous Contrast
NO EXPOSURE	Any CT without Intravenous Contrast
OUTCOME	Primary Outcome: Acute Kidney Injury based on each individual study's criteria Secondary Outcomes: 1. Use of renal replacement therapy 2. All-cause mortality Subgroup analyses: 1. ED setting 2. Timing of follow-up creatinine 3, Matching versus Non-matching study designs 4. Class of contrast material used
DESIGN	Met-analysis of observational studies: Retrospective cohort, Prospective cohort, Case-Control

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review explicitly address a sensible clinical question?	Yes. This was an important question with clearly defined parameters. However, studies differed in their definition of acute kidney injury, use of matching, contrast agent used, body area of CT included and study design (Table 1). Patients were matched in 7/28 (25%) of the included studies. It is unclear if comorbidities were similar in the unmatched studies.
Was the search for relevant studies detailed and exhaustive?	Yes. The search included Medline, Cochrane, CINAHL, Web of Science, Proquest, Academic Search Premier and Google Scholar. The search was not limited to the English language. The search strategy is presented in Figure E1. Conference abstracts from American College of Radiology, Society for Academic Emergency Medicine and the American Society of Nephrologists were searched from 2009-16. A funnel plot (Figure E2) and Eggers test did not reveal evidence of publication bias.
Was the risk of bias of the primary studies assessed?	Study quality was assessed using the Tool to Assess Risk of Bias in Cohort Studies (Table E1). Study quality was variable. Risk of bias was assessed as in the 28 included studies as: Low (n=7/28, 25%), Moderate (n=9/28, 32%), Serious (n= 10/28, 36%) and Critical (n=2/28, 7%). 43% (n=12/28) of studies were assessed as serious or critical risk of bias. 5 of the 28 studies included more that 10,000 patients and accounted for 51% of the patients in the AKI analysis. Of these 5 studies, risk of bias was assessed as: Low (n=3), Moderate (n=1) and Serious (n=1).
Were the selection and assessment of studies reproducible?	Unclear. Discussion was used to adjudicate decisions on study selection and quality. Inter-rater reliability on study selection and quality was not presented.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

There was significant heterogeneity for Acute Kidney Injury (I^2 = 65%, p < 0.001)
There was no significant heterogeneity for Renal Replacement Therapy (I^2 = 20%, p = 0.243)
There was no significant heterogeneity for All-cause Mortality (I^2 = 40%%, p =. 0.102)
An I^2 > 50% is generally considered to represent heterogeneity of study results
A random effects model was used to determine the summary odds ratio for each outcome

WHAT ARE THE OVERALL RESULTS OF THE REVIEW?

DEMOGRAPHIC DATA

	# Studies	# Patients
Acute kidney injury	26	92,795
Renal replacement therapy	13	67,714
All-cause mortality	9	36,252
TOTAL*	28	107,333
*Total is not additive. Some studies included more than 1 of the outcomes		

PRIMARY AND SECONDARY OUTCOMES (FIGURE 2)

	Contrast CT	Non-Contrast CT	Odds Ratio (95% CI)
Acute kidney injury	7.2% (3,448/48,118)	7.4% (3,316/44,677)	0.94 (0.83, 1.07)
Renal replacement therapy	0.6% (196/35,002)	0.7% (196/28,712)	0.83 (0.59, 1.16)
All-cause mortality	5.6% (1.095/19,549)	5.8% (966, 16,703)	1.0 (0.73, 1.36)
Odds Ratio = Odds of Outcome with Contrast CT/Odds of Outcome with Non-contrast CT GREEN = Statistically significant, RED = Not statistically significant			

Subgroup Analyses (Table 2):
There was a higher risk of AKI in the contrast group in patients receiving mixed contrast (Odds Ratio: 1.92, 95% CI (1.05, 3.52))
There was a lower risk of AKI in the contrast group in studies with an AKI definition of a greater than a 25% increase in creatinine (Odds Ratio: 0.67, 95% CI (0.46, 0.99))
There was no difference in the incidence of AKI for: Other types of contrast, matched studies, other AKI definitions, timing of creatinine follow-up and study setting.

DID THE REVIEW ADDRESS CONFIDENCE IN EFFECT ESTIMATES?

The confidence interval for the AKI outcome is fairly narrow given the large sample size. The confidence intervals for the RRT and all-cause mortality outcomes were fairly wide.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Unclear. The study only included adult patient so that generalization of the study results to pediatric patients is unclear. There was a slightly greater than 5% mortality in both of the study groups. It is unclear is this represents selection bias or if it is representative of the population of adults receiving a CT. In the subgroup analysis of ED patients, the incidence of AKI in the contrast CT group was 8.9% and the incidence of AKI in the non-contrast CT group was 9.2%. There was no statistically significant difference between the two groups (Odds Ratio: 0.79, 95% CI (0.58, 1.08).
Was follow-up complete and sufficiently long?	Unclear. Data on follow up and on either progression or resolution of AKI was not presented. An absolute or relative increase in serum creatinine is not a patient-oriented outcome. All-cause mortality is a patient oriented clinical outcome.
Is the exposure similar to what might occur in my patient?	Yes. Intravenous contrast is used frequently with CT. The most common pediatric use is for suspected appendicitis in patients with an equivocal abdominal ultrasound.
What is the magnitude of the risk?	There was no statistically significant increase in risk of either the primary or secondary outcomes. The risk difference for AKI was 0.2%, 95% CI (-0.1, 0.6%) in favor of the contrast CT group.
Are there any benefits that offset the risks associated with exposure?	There are obvious benefits to the use of intravenous contrast. In this study, there was not an increased risk of AKI, use of renal replacement therapy or all cause-mortality in the contrast CT group.

CLINICAL BOTTOM LINE

BACKGROUND: The rate of acute kidney injury (AKI) after CT with intravenous contrast has been highly variable in the literature. In addition, studies have differed considerably in their definition of AKI. Generally, AKI has been defined as a relative increase in creatinine of 25% or an absolute increase in creatinine by 0.3-0.5 within 48-72 hours of contrast administration. As a result of the potential risk of AKI, many institutions require measurement of serum creatinine prior to CT with contrast.

CLINICAL QUESTION: In adult patients undergoing CT with intravenous contrast when compared to CT without intravenous contrast, what is the risk of acute kidney injury defined as a relative or absolute increase in serum creatinine?

DESIGN/RISK OF BIAS: This was a meta-analysis of observational studies assessing the incidence of acute kidney injury in patients undergoing CT with intravenous contrast compared to those undergoing CT without intravenous contrast. The primary outcome of acute kidney injury was based on each individual study's criteria. Studies differed in their definition of acute kidney injury, use of matching, contrast agent used, body area of CT included and study design. Patients were matched in 7/28 (25%) of the included studies. It is unclear if comorbidities were similar in the unmatched studies.

An extensive search was conducted and no evidence of publication bias was identified. Study quality was variable. Risk of bias was assessed in the 28 studies as: Low (n=7/28, 25%), Moderate (n=9/28, 32%), Serious (n= 10/28, 36%) and Critical (n=2/28, 7%). 43% of studies (n=12/28) were assessed as serious or critical risk of bias. 18% (5/28) of the studies included more that 10,000 patients and accounted for 51% of the patients in the AKI analysis. Of these 5 studies, risk of bias was assessed as: Low (n=3), Moderate (n=1) and Serious (n=1). Inter-rater reliability on study selection and study quality was not presented.

PRIMARY RESULTS: 28 studies comprising 107,333 patients were included in the meta-analysis. There was a wide range of AKI in both study groups. The incidence of AKI in those receiving contrast was 2.1% to 26.4%. The incidence of AKI in those not receiving contrast was 1.3% to 35.8%%. The was no difference in the incidence of acute kidney injury, use of renal replacement therapy and all-cause mortality in those receiving a CT with intravenous contrast in comparison to those receiving a CT without contrast.

PRIMARY AND SECONDARY OUTCOMES (FIGURE 2)

	Contrast CT	Non-Contrast CT	Odds Ratio (95% CI)
Acute kidney injury	7.2% (3,448/48,118)	7.4% (3,316/44,677)	0.94 (0.83, 1.07)
Renal replacement therapy	0.6% (196/35,002)	0.7% (196/28,712)	0.83 (0.59, 1.16)
All-cause mortality	5.6% (1.095/19,549)	5.8% (966, 16,703)	1.0 (0.73, 1.36)

Odds Ratio = Odds of Outcome with Contrast CT/Odds of Outcome with Non-contrast CT
GREEN = Statistically significant, RED = Not statistically significant

In the preplanned subgroup analyses, there was a higher risk of AKI in the contrast group in patients receiving mixed contrast (1.92, 95% CI (1.05, 3.52)). There was a lower risk of AKI in the contrast group in studies with an AKI definition of a greater than 25% increase in creatinine (0.67, 95% CI (0.46, 0.99)). There was no difference in the incidence of AKI for: other types of contrast, matched studies, other AKI definitions, timing of creatinine follow-up and study setting.

APPLICABILITY: The large number of studies and patients included likely make the study's results applicable to adults meeting the study's inclusion and exclusion criteria. It is unclear if these results can be extrapolated to pediatric patients. There was a slightly greater than 5% mortality in both of the study groups. It is unclear is this represents selection bias or if it is representative of the population of adults receiving a CT.

In the subgroup analysis of ED patients, the incidence of AKI in the contrast CT group was 8.9% and the incidence of AKI in the non-contrast CT group was 9.2% (Risk Difference 0.3%). There was no statistically significant difference between the two groups (Odds Ratio: 0.79, 95% CI (0.58, 1.08)).

AUTHOR'S CONCLUSION: "In conclusion, our study found a lack of association between acute kidney injury and contrast-enhanced CT and no association with important patient-oriented and clinical outcomes, including the need for renal replacement therapy and mortality. The American College of Radiology ACR Manual on Contrast Media underscores this point and argues for a shift in language from contrast-induced nephropathy to postcontrast acute kidney injury, with the understanding that the acute kidney injury may be incidental rather than caused by the contrast. These findings are limited by the quality of included studies and by significant selection bias, including provider selection for contrast-enhanced CT. These observational data demonstrate that physician selection of patients to receive contrast-enhanced CT seems to add no additional risk of acute kidney injury, need for renal replacement therapy, or mortality. These findings are congruent with current assertions from the American College of Radiology."

POTENTIAL IMPACT: There are a number of study design and applicability issues with this meta-analysis. Studies differed in their definition of acute kidney injury, use of matching, contrast agent used, body area of CT included and study design. Study quality was variable with 43% of studies considered at serious or critical risk of bias. The study results are heavily weight by 5 studies that enrolled 51% of patients and there was a wide range in the incidence of AKI in both study groups.

"At the current time, it is the position of ACR Committee on Drugs and Contrast Media that contrast induced nephropathy is a real, albeit rare, entity. Published studies on contrast induced nephropathy have been heavily contaminated by bias and conflation. Future investigations building on recent methodological advancements are necessary to clarify the incidence and significance of this disease." (WEBLINK: American College of Radiology: Manual on Contrast 2018).

ACUTE SCROTAL PAIN:
TESTICULAR TORSION DECISION RULE

In patients younger than 18 years of age who present with acute scrotal pain and suspected testicular torsion, do clinical findings accurately in identifying those with and without testicular torsion?

Maria Lame M.D., Dennis Heon M.D.
July 2014

Barbosa JA, Tiseo BC, Barayan GA, Rosman BM, Torricelli FC, Passerotti CC, Srougi M, Retik AB, Nguyen HT.

DEVELOPMENT AND INITIAL VALIDATION OF A SCORING SYSTEM TO DIAGNOSE TESTICULAR TORSION IN CHILDREN

J Urol. 2013 May;189(5):1859-64.
PubMed ID: 23103800

STUDY DEFINITIONS	
POPULATION	Derivation Set Inclusion: 3 months-18 years, acute scrotal pain (< 1 week) Exclusion: Symptoms > 1 week, prior scrotal disease/surgery Validation Set Inclusion: Chart review of ICD-9 = Orchitis, epididymitis, torsion of testis, torsion of testicular appendage Exclusion: Incomplete data or non-acute presentation Setting: Single pediatric emergency department (Brazil). 1/2009-1/2012
RULE	History and clinical examinations factors (structured data collection sheet)
REFERENCE STANDARD	Non-surgical cases: Scrotal doppler ultrasound Surgical cases: Post-operative diagnosis
OUTCOME	Rule characteristics
DESIGN	Observational: Prospective cohort (derivation), Retrospective cohort (validation)

ARE THE RESULTS VALID?	
Were all important predictors included in the derivation process?	Yes. The list of patient history and exam characteristics was inclusive of all clinically important predictors. The selected predictors were based on review of existing medical literature.
Were all important predictors present in significant proportion of the study population?	Unclear. Predictor prevalence was not described
Were the outcome event and predictors clearly defined?	Yes. Testicular torsion was clearly defined. The criterion standard for non-operative cases was doppler ultrasound. The criterion standard for surgical cases was post-operative diagnosis. Some of the predictors, particularly the physical exam findings could be open to interpretation. All predictors included in the final rule had good inter-rater reliability (kappa > 0.6)
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Yes. The urologist documenting the presence or absence of predictors on a standardized data entry form were blinded to the outcome event. The data entry forms were completed prior to obtaining the Doppler ultrasound or the postoperative diagnosis. Unclear. It is unclear whether those assessing the outcome event were blinded to the presence of the predictors. The radiologists reading the Doppler ultrasound may have been aware of clinical findings. It is unlikely that the urologist performing the surgery were blinded to presence of predictors. It's unclear if the same urologist performing the data collection was the operating surgeon. However, it is unlikely that the outcome assessment could be biased by the potential lack of blinding. In the validation phase of the study. It is unclear if the data abstractors were blinded to the outcome event.
Was the sample size adequate (including an adequate number of outcome events)?	The study authors predetermined the number of outcome events needed to create the prediction model. 50 outcome events were required in order to allow 10 events per variable on a 5-variable logistic regression. 51 patients with testicular torsion were enrolled.

WHAT ARE THE RESULTS?

How well did the rule correctly identify patients <u>with</u> the primary outcome? How precise was this measurement? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

How well did the rule correctly identify patients <u>without</u> the primary outcome? How precise was this measurement? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

<u>Prevalence</u> (Testicular Torsion): 51/338 = 15%

<u>TWIST Rule (Cutoff = 2)</u>
Sensitivity: 100% 95% CI (91-100%)
Specificity: 82% 95% CI (76-86%)
Predictive value (+) Rule: 49% 95% CI (39-59)
Predictive value (-) Rule: 100% 95% CI (98-100))

<u>TWIST Rule (Cutoff = 5)</u>
Sensitivity: 76% 95% CI (62-87%)
Specificity: 100% 100% CI (98-100%)
Predictive value (+) Rule: 100% 95% CI (89-100)
Predictive value (-) Rule: 96% 95% CI (93-98)

<u>Accuracy</u> (Area under the receiver operating characteristic curve), 0.983, 95% CI (0.971, 0.994)

How would use of the rule impact resource utilization?

<u>Risk Stratification</u>
Low Risk: Score ≤ 2 (69.2%): No ultrasound, No OR
Intermediate Risk: Score 3-4 (19.2%): Ultrasound +/- OR
High Risk: Score ≥ 5 (11.5%): OR, No ultrasound

Following the rule, the low and high-risk group (69.2% + 11.5% = 80.7%) would not get an ultrasound. If 100% got an ultrasound prior to use of the rule then rule would reduce ultrasound utilization by 80%.

Was there an internal statistical validation of the results? How did it compare to the primary results?

Yes. A retrospective internal and external statistical validation was completed. Results of the derivation and internal validation sets were very similar.

<u>Internal Validation:</u> (AUC 0.996 95% CI 0.988-1.0)
Low risk: 77 of 116 (66.3%)
Intermediate risk: 19 of 116 (16.3%)
High risk: 20 of 116 (17%)

	SCORE = 2	SCORE = 5
Sensitivity	100% (88-100)	54% (37-70)
Specificity	97% (90-99)	100% (94-100)
Predictive Value (+) Rule	95% (81-99)	100% (80-100)
Predictive Value (-) Rule	100% (94-100)	82% (73-89)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see Appendix)	This is a stage IV clinical decision rule. It was derived and then retrospectively validated. The external validation set included only patients with testicular torsion so rule characteristics could not be performed. No impact analysis was included. This rule requires further broad validation before it can be applied clinically
Does the rule make clinical sense?	Yes. The rule does make sense; the five predictors are salient factors currently considered in patients with possible testicular torsion.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	The decision rule is easy to follow though some of the predictors are somewhat subjective. This is particularly true for the physical exam findings of swelling and a “hard” testicle. The kappa of the predictors between urologists and non-urologists in the final rule were moderate. Non-urologist findings were abstracted from the medical record (i.e. they did not use the structured data collection form)
Is the rule applicable to the patients in my practice?	Unclear. Demographic characteristics were not provided. The setting is a tertiary care pediatric emergency department.
What are the benefits of applying the rule to my patients?	If broadly validated, applying the TWIST rule could potentially decrease the utilization of scrotal ultrasound by 80%
What are the risks of applying the rule to my patients	No patients with testicular torsion were missed in the low risk group. The lower limit of the 95% confidence interval for sensitivity and predictive value of a negative rule indicates the possibility of missed testicular torsion. Limiting ultrasound utilization could also decrease identification of other diagnoses associated with acute scrotal pain such as epididymitis and torsion of the appendix testes.

CLINICAL BOTTOM LINE

BACKGROUND: The majority of patients presenting with acute scrotal pain do not have testicular torsion. Identification of factors indicating a low risk of testicular torsion could potentially decrease the utilization of scrotal ultrasound.

CLINICAL QUESTION: In patients younger than 18 years of age who present with acute scrotal pain and suspected testicular torsion, do clinical findings accurately in identifying those with and without testicular torsion?

DESIGN/VALIDITY: This study aimed to derive and validate a clinical scoring system for the diagnosis of testicular torsion in pediatric patients with acute scrotal pain. The scoring system was prospectively derived and underwent retrospective internal and external validation. There were 338 patients in the derivation group, 51(15%) of which had testicular torsion.

There are a number of validity concerns. There is not an accurate description of the study population. The study took place in pediatric emergency departments but those assessing the presence of the rule parameters were urologists. In addition, some of the clinical predictors were subjective with only moderate inter-rater reliability between urologists and non-urologists.

This TWIST Rule in the derivation set was able to identify those at low risk of testicular torsion (Predictive Value of Negative Rule (Score ≤ 2) 100% 95% CI (98-100%). In addition, the rule has the potential to reduce ultrasound utilization by 80% in the study population. Limiting ultrasound utilization would also decrease identification of other diagnoses such as epididymitis and torsion of the appendix testes. The rule performance was similar in the retrospective, internal validation set.

TWIST RULE*			
Testicular swelling	2	Low Risk: Score ≤ 2	No ultrasound
Hard testis on palpation	2	Intermediate Risk: Score 3-4	Ultrasound
Nausea or emesis	1	High Risk: Score ≥ 5	OR w/o Sono
High riding testis	1	Range: 0-7	
Absent cremasteric reflex	1		
*Testicular Workup for Ischemia and Suspected Torsion			

APPLICABILITY: The study's results may not be applicable to non-urologists. This is a stage IV clinical decision rule. It was derived and then retrospectively validated internally. The external validation set included only patients with testicular torsion so rule characteristics could not be performed. No impact analysis was included. The rule requires further validation before it can be applied clinically

AUTHOR'S CONCLUSION: "Our scoring system could be a valuable tool for clinical diagnosis of testicular torsion. Risk stratification could help decrease orders for ultrasound in up to 80% of TT cases, and more than 50% of cases could have ischemia time abbreviated. Despite encouraging results with high positive and negative predictive values, further validation of this scoring system is necessary."

POTENTIAL IMPACT: There were a number of validity concerns with the derivation of the rule. These concerns should be address and the rule should be broadly validated before it can be applied clinically.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

RENAL STONES:
POINT OF CARE ULTRASOUND (HYDRONEPHROSIS)

In ED patients with suspected renal colic, what are the test characteristics of bedside ultrasound by clinicians with a wide range of experience for detecting hydronephrosis as compared to non-contrast CT scan?

Katrina Knapp D.O., Alvira Shah M.D.
June 2015

Herbst MK, Rosenberg G, Daniels B, Gross CP, Singh D, Molinaro AM, Luty S, Moore CL.

EFFECT OF PROVIDER EXPERIENCE ON CLINICIAN-PERFORMED ULTRASONOGRAPHY FOR HYDRONEPHROSIS IN PATIENTS WITH SUSPECTED RENAL COLIC

Ann Emerg Med. 2014 Sep;64(3):269-76.
PubMed ID: 24630203

STUDY DEFINITIONS	
POPULATION	Inclusion: Patients > 18 years of age presenting to the ED with suspected renal colic for which the clinician intended to obtain a CT scan Exclusion: Prior CT scan with known results, known renal disease (chronic kidney disease, renal transplant, polycystic kidney disease), trauma, non-English speaking, incarcerated, ultrasound uninterpretable, CT not obtained Setting: 2 associated ED's: 1 urban academic, 1 community, 7/2010-11/2012
TEST	Clinician performed bedside ultrasound Clinician experience categorized as a. Attending with ultrasound fellowship training b. Attending without ultrasound fellowship training c. Non-attending with > 2 weeks of ultrasound training d. Non-attending with < 2 weeks of ultrasound training
REFERENCE STANDARD	Non-contrast CT scan
OUTCOME	Test characteristics for point of care ultrasound
DESIGN	Observational: Prospective cohort

ARE THE RESULTS VALID?	
Did participating patients present a diagnostic dilemma?	Yes. Patients they presented a diagnostic dilemma. Patients were suspected of having renal colic. It is unclear if patients with a prior history of renal stones was included.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. Current guidelines recommend CT scan abdomen/pelvis without contrast as the initial diagnostic test for acute flank pain with suspicion of stone disease.
Were those interpreting the test and reference standard blind to the other results?	Yes. The bedside renal ultrasound was performed prior to the CT scan. The radiologist was blinded to the results of the bedside ultrasonography when interpreting the CT. Ultrasonographers were not blinded to the patients' symptoms. About 80% of the examinations were performed by the provider directly involved in patient care. A post hoc analysis was performed to detect any significant differences in test characteristics according to whether the clinician performing the ultrasound was directly involved in the care of the patient.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	Yes. All patients who had a bedside ultrasound had a CT scan without contrast.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

		HYDRONEPHROSIS		
		YES	NO	
ULTRASOUND	POSITIVE	231	94	325
	NEGATIVE	87	258	345
		318	352	670

Prevalence: 318/670 = 47%
Sensitivity: 231/318 = 72%
Specificity: 258/352 = 73%
PV (+): 231/325 = 71%
PV (-): 258/345 = 75% (75% of the patients with a negative ultrasound did not have hydronephrosis. Alternatively 25% of the patients with a negative ultrasound had hydronephrosis 1-PV(-) = 1 – 0.75 = 0.25)

Pretest Probability in this study = 50%
Post Test Probability with a Positive Test = 71%
Post Test Probability with a Negative Test = 25%

LR (+): Test (+)/Disease (+) = 231/318 = 0.73 = 2.7
Test (+)/Disease (-) 94/352 0.27
2.7 times more likely with a positive ultrasound to have hydronephrosis than to not have hydronephrosis

LR (-): Test (-)/Disease (+) = 87/318 = 0.27 = 0.37
Test (-)/Disease (-) 258/352 0.73
0.37 times more likely with a negative US to have hydronephrosis than to not have hydronephrosis.
1/LR (-) = 2.7 times less likely with a negative ultrasound to have hydronephrosis
The likelihood ratio of a positive and negative are essentially equivalent

	ATTENDING WITH US FELLOWSHIP	ALL OTHERS
Sensitivity	92.7% (83.8-96.9)	68.4% (59.1-76.5)
Likelihood Ratio (+) Test	4.97 (2.9-8.51)	2.42 (1.98-2.95)
Likelihood Ratio (-) Test	0.08 (0.03-0.23)	0.44 (0.37-0.53)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	Kappa (level of agreement beyond chance) was 0.87 of inter-observer reliability of CT data extraction. Kappa was not done on CT scan readings. There was no Kappa for the ultrasound interpretation. The ultrasound interpretations were subjective, so it is not known if it will be able to be reproduced. Attendings with an ultrasound fellowship had a higher sensitivity compared to all others.
Are the study results applicable to the patient in my practice?	Possibly. Average age of patients was 46, which is significantly higher than what we see in the pediatric ED. It is not clear what the definition of “suspected” renal colic was amongst physicians.
Will the results change my management strategy?	Post test probability of a (+) test was 71%. Post test probability of a (-) test was 25%, so you would be missing hydronephrosis on 25% of patients with suspected renal colic.
Will patients be better off as a result of the test?	Benefits include a reduction in radiation exposure and a decrease time spent in ED waiting for CT scan and read by radiologist. Harms include missing hydronephrosis as a possible result of a kidney stone which may require intervention (medical versus surgical management). Unlike CT scan, ultrasound does not detect the size or location of the renal stone or potential alternative diagnoses.

CLINICAL BOTTOM LINE

BACKGROUND: Current guidelines recommend CT scan as the initial diagnostic test for acute flank pain with suspicion of stone disease. The use of CT for the diagnosis of suspected renal stones has increased by a factor of 10 over the past 15 years in the United States. Despite it being a sensitive test for detecting kidney stones, there is exposure to ionizing radiation. Also, CT scanning is expensive and time consuming for patients waiting for their imaging and results. Ultrasound offers a safe imaging alternative for renal colic, which has been shown to be accurate when performed by experienced users. Bedside point of care ultrasound is being utilized more frequently and is incorporated into residency training programs across the US with emergency medicine guidelines set forth by ACEP.

CLINICAL QUESTION: In ED patients with suspected renal colic, what are the test characteristics of bedside ultrasound by clinicians with wide range of experience for detecting hydronephrosis as compared to non-contrast CT scan?

DESIGN/VALIDITY: This study enrolled 670 patients over 18 years of age who were suspected of having renal colic. Each subject who was enrolled had an ultrasound to detect hydronephrosis by 4 different levels of trained ultrasound clinicians. The four different levels we “attending physicians with fellowship training,” “attending physicians without fellowship training,” “ultrasound experienced non-attending physician clinicians,” and “ultrasound inexperienced non attending physicians.” The diagnosis of hydronephrosis on ultrasound was categorized as: none, mild, moderate, or severe. The diagnosis was determined subjectively by the primary ultrasonographer. There was no additional ultrasound training provided as part of this protocol. All subjects enrolled also underwent CT scan without contrast after the ultrasound. The test characteristics of hydronephrosis on ultrasound was compared to both the presence of hydronephrosis and presence of renal stone on CT scan of abdomen/pelvis without contrast. It is important to note that 5.5% of patients in this study had hydronephrosis on CT without the presence of a renal stone (? already passed the stone) and 6.0% had a stone on CT without the presence of hydronephrosis. In addition, the CT scan can also identify the presence, size and location of a stone and alternative diagnsoses.

There did not seem to be any risk of bias concerns in this study. All participating patients in the study presented with a diagnostic dilemma of having suspected renal colic. They did not define what clinical signs or symptoms the patient exhibited for which put them at risk for a diagnosis of renal colic. The investigators compared the test to the appropriate reference standard of CT scan without contrast for which all patients enrolled in the study obtained for comparison. The radiologists who interpreted the CT were blinded to the results of beside ultrasound. About 80% of clinicians who performed the bedside US were directly involved the patients care. A post hoc analysis was performed to detect any significant differences in test characteristics between clinical operators who directly involved in the patients care and those who were not.

PRIMARY RESULTS: Any hydronephrosis detected on clinician performed ultrasonography was 72% sensitive and 73% specific, with a positive likelihood ratio of 2.72 and a negative likelihood ratio 0.373. Attending physicians with fellowship training compared with other users had significantly better sensitivity, 92.7% versus 68.4% with positive likelihood ratio 4.97 and negative likelihood ration of 0.08. The test characteristics for providers who were directly involved in the care of the patients versus those who were not were not statistically significant then those not directly involved.

When subgroup analysis was performed on whether moderate or greater hydronephrosis was present, the overall specificity of clinician-performed ultrasonography for hydronephrosis observed on CT was 94% but sensitivity decreased to 31% and was not significantly different between operator groups.

APPLICABILITY: This was an adult study and it is unclear if the results are generalizable to younger children though they should be applicable to adolescents with suspected renal colic.

AUTHOR'S CONCLUSION: "Overall, ultrasonography performed by emergency clinicians was moderately sensitive and specific for detection of hydronephrosis as seen on CT in patients with suspected renal colic. However, presence or absence of hydronephrosis as determined by emergency physicians with fellowship training in ultrasonography yielded more definitive test results. For clinicians without fellowship training, there was no significant difference between groups in the predictive accuracy of the application according to experience level."

POTENTIAL IMPACT: Sensitivity and specificity were lower than expected. The sensitivity and specificity was found to be higher for ultrasound fellowship trained provider than other provider groups. It is possible to avoid CT scans in patients without hydronephrosis on point of care ultrasound abdomen/pelvis and send the patient home with good pain control and encourage oral hydration with return precautions if an infected renal stone is not suspected. It is unclear if those with unilateral hydronephrosis can be managed without a CT scan.

URINARY TRACT INFECTION: ADVERSE EVENT RULE DERIVATION

In febrile infants aged 29 to 60 days who have a urinary tract infection, can patient characteristics and laboratory results adequately identify those with and without adverse events and bacteremia?

Janienne Kondrich, M.D., Michael Mojica, M.D.
January 2011

Schnadower D, Kuppermann N, Macias CG, Freedman SB, Baskin MN, Ishimine P, Scribner C, Okada P, Beach H, Bulloch B, Agrawal D, Saunders M, Sutherland DM, Blackstone MM, Sarnaik A, McManemy J, Brent A, Bennett J, Plymale JM, Solari P, Mann DJ, Dayan PS; American Academy of Pediatrics Pediatric Emergency Medicine Collaborative Research Committee.

FEBRILE INFANTS WITH URINARY TRACT INFECTIONS AT VERY LOW RISK FOR ADVERSE EVENTS AND BACTEREMIA.

Pediatrics. 2010 Dec;126(6):1074-83.
PubMed ID: 21098155

STUDY DEFINITIONS	
POPULATION	Inclusion: Patients 29-60 days of age Urine cultures. Single pathogen with: 1. 1,000 CFU/mL: suprapubic specimen OR 2. 50,000 CFU/mL: catheterized specimen OR 3. 10,000-50 000 CFU/mL: catheterized specimen with positive urinalysis Positive urinalysis: 1. Any organisms on Gram-stain OR 2. Trace or greater result for leukocyte esterase or nitrite OR 3. ≥ 5 WBC/hpf (microscopy) or per L (hemocytometer) Exclusion: 1. Transfer from other hospitals with laboratory results 2. Urine specimens not obtained by suprapubic aspiration or catheterization 3. Urine cultures that grew multiple organisms 4. No temperature ≥ 38.0°C in the ED or at home within 24 hours of ED visit 5. Contaminants: L*actobacillus*, *Micrococcus*, diptheroids, *Bacillus* species and *Staphylococcus epidermidis* Setting: 20 centers (16 tertiary care pediatric EDs and 3 general EDs in the United States and 1 Canadian tertiary care ED) of the Pediatric Emergency Medicine Collaborative Research Committee of the AAP. 1/1995-5/2006
RULE PARAMETERS	Structured data collection form for chart abstraction
REFERENCE STANDARD	Adverse Events: Death Shock Bacterial meningitis ICU/Step down admission or transfer Ventilatory support (including CPAP, BiPAP) Surgical Intervention Other substantial adverse event (iatrogenic complications excluded) Bacteremia: Growth of a pathogen (Contaminants: *Bacillus* species, *Propionibacterium acnes*, or non–*S aureus)*
OUTCOME	Rule characteristics: Adverse event rule, Rule characteristics: Bacteremia rule
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. The list of patient characteristics and laboratory results examined were extensive and inclusive of almost all clinically important predictors. In addition, it may have been valuable to include the rate of viral infection (particularly RSV infection) as these were not counted as acute concomitant disease (defined as acute, focal infectious processes distinct from the urinary tract infection).
Were all important predictors present in significant proportion of the study population?	Yes. With the except for seizure (20/1895 (1%)) and acute concomitant disease (25/1895 (1.3%).
Were the outcome event and predictors clearly defined?	Yes and No. Most of the outcome events were clearly delineated, particularly the definitions used for both shock and bacterial meningitis. However, neither ICU admission/ transfer 37/51 (72%) nor other complications 11/51 (22%), two entities that made up the majority of the adverse events, were clearly defined.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Not explicitly stated. It is unclear of those performing the chart review were blinded to the outcome event.
Was the sample size adequate (including an adequate number of outcome events)?	The study authors predetermined the number of adverse events and cases of bacteremia needed to create prediction models. Approximately 50 adverse events were required for a model that was 100% sensitive with a 95% CI lower boundary of 94%. This goal was met with 51 adverse events. For the bacteremia model, 100 patients with bacteremia were required to create a model that was 95% sensitive with a 95% CI lower boundary of 89%. The study population included 107 cases of bacteremia.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

Risk of Adverse Events:
51/1,842 = 2.8% (2.1-3.6%)

Low Risk for Adverse Events Rule
1. Clinically ill in the ED
2. High-risk past medical history

Sensitivity: 98.0% 95% CI (88.2, 99.9%)
One patient was treated empirically for bacterial meningitis after CSF studies were lost. Subsequent CSF (24 hours after antibiotics) was not suggestive of meningitis. The patient had an unremarkable clinical course.

Risk of Bacteremia:
123/1,877 = 6.6% (4.9-7.1%)

Low Risk of Bacteremia Rule (Absence of all 4 factors)
1. Clinically ill in ED
2. High-risk past medical history
3. Bands ≥ 1,250 cells/μL
4. ANC < 1, 500 cells/μL.

Sensitivity: 77.2% (95% CI: 68.6 – 84.1%)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

Low Risk for Adverse Events Rule
Negative predictive value of 99.9% (95%CI: 99.5 – 100%)
1/1,000 with negative rule with AE (lower limit 1/250)

Low Risk of Bacteremia Rule
Negative predictive value of 96.8% (95%CI 95.3 – 97.8%)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

In the study population, 90.7% (1,719/1,895) of the patients were hospitalized; 65% met the low risk criteria for adverse events. 91% of adverse events and 88% of bacteremia was identified within 24 hours. Use of the adverse event rule could decrease hospitalization of infants with febrile UTIs by approximately 65%. Admission to a short stay unit or observation unit may also be an option for these patients. The authors were ultimately not successful in creating a clinical prediction rule that would identify those infants at very low risk of bacteremia.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

Cross validation was performed but the results were not presented.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see appendix)	☐ I ☐ II ☐ III ■ IV This is a stage IV rule that has been derived only or validated only in split samples, large retrospective databases or by statistical methods. Stage IV rules require further validation before it can be applied clinically
Does the rule make clinical sense?	Yes. The rule created for adverse events makes clinical sense. Both predictors (clinical appearance in the ED and high risk past medical history) are salient factors currently considered by ED practitioners when evaluating febrile infants.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	The predictor “clinical ill in the ED” includes subjective parameters such as ill appearing, dehydrated and respiratory distress. Due to the retrospective nature of the data collection interrater reliability was not assessed. It is unclear that these factors could be consistently applied.
Is the rule applicable to the patients in my practice?	Yes. This study included patients from 19 institutions across the US and Canada, from both tertiary care pediatric and general emergency departments. The study population included patients from communities in New York City similar to the population seen at Bellevue and NYU.
Will the rule results change my management strategy?	No. Not at this time. The rule did not adequately identify those with bacteremia (Sensitivity 77.2%)
What are the benefits of applying the rule to my patients?	For young infants with known febrile urine tract infections the rule could decrease hospitalization or length of hospitalization and its associated risks by over fifty percent.
What are the risks of applying the rule to my patients?	The rule may incorrectly classify an infant as very low risk and result in a serious adverse event.

CLINICAL BOTTOM LINE

BACKGROUND: The majority of febrile infants with urinary tract infections demonstrate evidence of pyelonephritis on renal scans. In the past these infants were admitted for intravenous antibiotics. Recent evidence suggests that older infants and children may be managed with parenteral antibiotics as outpatients with a comparable risk of both long and short-term sequelae (Hoberman Pediatrics 1999, PubMed ID: 10390264). In this study, less than 0.5% of patients were less than 4-7 weeks and the proportion of patients less than 3 months of age could not be determined from the data presented.

CLINICAL QUESTION: In febrile infants aged 29 to 60 days who have a urinary tract infection, can patient characteristics and laboratory results adequately identify those with and without adverse events and bacteremia?

DESIGN/RISK OF BIAS: This multicenter, retrospective cohort study sought to identify predictors of adverse events and bacteremia in infants aged 29 to 60 days with febrile urinary tract infections. The study included 51/1,842 (2.8%, 95% CI (2.1-3.6%)) infants with adverse events and 123/1,877 = 6.6%, 95% CI (4.9, 7.1%) infants with bacteremia. This a well-designed retrospective chart review. It is unclear why bacteremia was assessed independently and not included as an adverse event.

PRIMARY RESULTS: Adverse events in this population were rare occurring in approximately 3%. 91% of adverse events and 88% of bacteremia was identified within 24 hours. Approximately 50% of adverse events were identified in the emergency department. The value of the rule to “predict” these events is unclear. It would have been more valuable to develop a rule for those who were considered well in the ED and subsequently developed an adverse event.

The study was successful in creating a clinical prediction rule that identified infants at very low risk for adverse events. Infants who were not clinically ill at the time of ED presentation and did not have high-risk past medical history were correctly identified as low risk for adverse events. (Negative predictive value 99.9%, 95% CI (99.5 – 100%)). Approximately 1 per 1,000 infants with a negative rule had an adverse event with an upper confidence limit of 1 per 240. 65% met the low risk criteria for adverse events. Use of the adverse event rule could decrease hospitalization of infants with febrile UTIs by approximately 65%.

The study was not successful in developing a rule to identify a rule to identify infants at low risk for bacteremia (Negative predictive value of 96.8%, 95% CI (95.3, 97.8%)). While the pre-rule rate of bacteremia was 2.8%, the rate of bacteremia in those with a negative rule was 3.2% with a 95% confidence interval upper limit of 4.7%.

APPLICABILITY: The use multiple centers likely makes this rule applicable to the majority of patients in emergency department setting. The applicability to other settings is unclear. The retrospective data collection does not allow for the determination of inter-rater reliability of the rule parameters. The bacteremia rule was unsuccessful. The adverse events rule has the potential to decrease admissions. However, this is a level IV clinical decision rule (derivation only) and requires validation before it can be applied in the clinical setting.

FEBRILE INFANT WITH UTI: LOW RISK OF ADVERSE EVENTS RULE
NO HIGH-RISK PAST MEDICAL HISTORY
GU abnormalities
Previous infection (UTI, bacteremia, meningitis)
Previous laboratory evaluation for fever
Premature (< 37 weeks' gestational age)
Complex heart, lung, metabolic or neurologic disease
NOT CLINICALLY ILL IN THE ED
Ill appearing
Dehydrated
Respiratory Distress
Concomitant illness disease* (focal infection other than UTI): Pneumonia, bronchiolitis, cellulitis, septic arthritis, osteomyelitis. Excluded: Gastroenteritis, acute otitis media

AUTHOR'S CONCLUSION: "We derived a highly accurate prediction model that identifies a group of febrile infants aged 29 to 60 days with UTIs at very low risk for adverse events. We attempted but were unsuccessful in deriving a very low risk model to identify infants who had bacteremia. Initiating antimicrobial therapy and brief hospitalization (e.g., 24 hours), within which time frame most bacteremia will be identified, seems appropriate management for this group of infants. Outpatient management with long-acting intramuscular antibiotics and close follow-up could also be considered after a period of observation. Future research should attempt to validate the prediction model for adverse events and continue to assess the safety and feasibility of alternative management strategies for these young febrile infants with UTIs."

POTENTIAL IMPACT: The ability to determine which infants with a febrile urinary tract infection are at low risk for bacteremia or an adverse event would be valuable. The study was unable to accurately predict those a low risk for bacteremia. The study was better able to identify those at low risk for advents and potentially decrease admissions. However, 50% of adverse events were identified in the ED potentially limiting the application of the rule and the rule has not been validated.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

URINARY TRACT INFECTION: DECISION RULE DERIVATION

In febrile females under 2 years of age, can components of the history and physical examination be used to accurately identify those at low risk for a urinary tract infection?

Rachel Kowalsky, M.D MPH., Michael Tunik, M.D
December 2008

Gorelick MH, Shaw KN.

CLINICAL DECISION RULE TO IDENTIFY FEBRILE YOUNG GIRLS AT RISK FOR URINARY TRACT INFECTION.

Arch Pediatr Adolesc Med. 2000 Apr;154(4):386-90.
PubMed ID: 10768678

STUDY DEFINITIONS	
POPULATION	Inclusion: Girls < 2 years, presented to ED, fever (≥ 38.3°C) Children with a possible, but not definitive, source of fever, such as upper respiratory tract infection, gastroenteritis, otitis media, or nonspecific viral syndrome Exclusion: Children with a definitive focus of infection to explain the fever. (meningitis, pneumonia by chest radiograph, cellulitis, and streptococcal pharyngitis), specific viral infections (varicella, Coxsackie disease, herpetic stomatitis), febrile disease (Kawasaki syndrome, Henoch-Schonlein purpura). Setting: Single Children's Hospital ED, Enrollment period not reported
RULE PARAMETERS	Candidate Predictor Variables Demographic: Age (< 12 vs ≥ 12 months), race (white vs nonwhite), race (adjusted for residence and insurance type) Historical: Duration of fever ≥ 2 days, any gastrointestinal symptoms, any urinary symptoms. past history, absence of ill contacts Physical examination: Temperature ≥ 39°C. ill general appearance, any tenderness absence of an alternative source of fever
REFERENCE STANDARD	Urinary Tract Infection: A positive urine culture with pure growth of ≥ 10^4 colonies/mL of a pathogenic species of bacteria obtained by catheterization
OUTCOME	Rule characteristics
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. Candidate historical predictors included age, race, duration of fever, presence of GI and urinary tract symptoms, past history of UTI, and absence of ill contacts. Candidate physical examination findings included height of fever, ill appearance, abdominal tenderness, and absence of an alternative fever source.
Were all important predictors present in significant proportion of the study population?	Yes. Prevalence of each predictor can be found in an antecedent study. Those that were not present in significant proportion (such as malodorous urine) were not included in the logistic regression analysis.
Were the outcome event and predictors clearly defined?	Yes. The outcome of interest was UTI, defined as a positive urine culture with pure growth of $\geq 10^4$ colonies/mL of a pathogenic species of bacteria. All urine specimens were obtained by urethral catheterization.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Yes. Those who collected predictor variables prospectively were blinded to the urine culture results. Foreknowledge of the predictors would not have influenced the objective urine culture results. Those assessing the outcome data (positive or negative urine culture) were unlikely to have knowledge of the patient's clinical presentation.
Was the sample size adequate (including an adequate number of outcome events)?	Yes. UTI was present in 63/1,469 (4.3%). There were 1,151 patients (with 56 UTIs) with complete data for all variables included in the regression analysis. In general, a 10:1 ratio of outcomes to predictors variables is considered adequate for logistic regression. There were 56 UTI's and 5 predictors.

WHAT ARE THE RESULTS?

DEMOGRAPHICS

N = 1,469, 63 (4.3%) with UTI.
N = 1,151, 56 (4.8%) with UTI in the regression analysis
Mean age 11.0 ± 6.2 months.
African American (84%), White (12%), Other (4%)
Well appearing: 68%
Potential source of fever on examination: 77%

RULE PREDICTORS	ADJUSTED ODDS RATIO
White race	7.5
Age < 12 months	3.0
Temperature ≥ 39.0°C	2.6
Absence of potential source of fever	2.4
Duration of fever ≥ 2 days	2.0
A Positive Rule is ≥ 2 of the risk factors A Negative Rule is < 2 of the risk factors	

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

Sensitivity: 95%, 95% CI (85, 99%)
Predictive Value of a (-) Rule: 0.8%, 95% CI (0.2, 2.5%)
Likelihood Ratio of a (+) Rule: 1.35, 95% CI (1.21, 1.43)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

Specificity: 31%, 95% CI, (28, 34%)
Predictive Value of a (+) Rule: 6.4%, 95% CI (4.8, 8.3%)
Likelihood ratio of a (-) Rule: 0.18, 95% CI (0.06, 0.49)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

If a urine culture was obtained only from girls with a score of ≥ 2, 30% of the urine cultures could have been avoided.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

No internal validation was performed.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (See Appendix)	☐ I ☐ II ☐ III ■ IV This is a stage IV clinical decision rule. A stage 4 rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. A stage IV rule requires further validation before it can be applied clinically
Does the rule make clinical sense?	Yes. The predictor variables make clinical sense, and the rule is easy to use.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. 4 of the 5 predictors present in the rule (race, age, duration fever and temperature) are objective. The 5th predictor, “absence of another source of fever” may not be as objective. Inter-rater reliability for this predictor was not presented.
Is the rule applicable to the patients in my practice?	The rule may not work as well in the Bellevue hospital center setting, as one of the predictors (white race) is not present in our population in high proportion. Racial and ethnic factors are known to affect the prevalence of UTI.
Will the rule results change my management strategy?	The variables in the rule are ones that are typically considered in the evaluation of febrile females. The rule requires further validation before it can be applied.
What are the benefits of applying the rule to my patients?	The rule could potentially eliminate about 1/3 of urinary catheterizations in febrile young females.
What are the risks of applying the rule to my patients?	The potential risk of applying the rule is missing those with a UTI. The sensitivity of the rule was 95% with a lower limit of the 95th confidence interval of 85%.

CLINICAL BOTTOM LINE

BACKGROUND: The most common serious bacterial infection in infants and young children is urinary tract infection (UTI). Females are at higher risk. It is often difficult to distinguish between the clear majority of febrile infants who will a benign viral illness a those with a UTI. Prior studies have indicated that the risk of UTI can be determined by demographic characteristics and elements of the history and physical examination.

CLINICAL QUESTION: In febrile females under 2 years of age, can components of the history and physical examination be used to accurately identify those a low risk for a urinary tract infection?

DESIGN/RISK OF BIAS: This was a well-designed derivation of a clinical decision rule that included 1,151 febrile female infants and young children of which 56 (4.8%) had a UTI. The rule was derived to maximize sensitivity at a cost to specificity.

PRIMARY RESULTS: The presence of 2 or more variables predicted a positive urine culture with a Sensitivity: 95%, 95% CI (85, 99%) and a Predictive Value of a Negative Rule of 0.8%, 95% CI (0.2, 2.5%). Those with less than two of the rule variables predicted the absence of a urinary tract infection with a Specificity of 31%, 95% CI, (28, 34%) and a Predictive Value of a Positive Rule of 6.4%, 95% CI (4.8, 8.3%). Essentially, the rule stratified a group of febrile female infants and young children with a 4.8% risk of UTI into a low-risk group (Rule Score < 2, UTI risk of 0.8%) and a high-risk group (Rule Score ≥ 2, UTI risk of 6.4%). If a urine culture was obtained only from girls with a score of ≥ 2, 30% of the urine cultures could potentially have been avoided.

RULE PREDICTORS	ADJUSTED ODDS RATIO
White race	7.5
Age < 12 months	3.0
Temperature ≥ 39.0°C	2.6
Absence of potential source of fever	2.4
Duration of fever ≥ 2 days	2.0
A Positive Rule is ≥ 2 of the risk factors A Negative Rule is < 2 of the risk factors	

APPLICABILITY: The study population with 84% African American. Given that one of the predictor variables was white race it is unclear if the study's results would be generalizable to populations with different ethnic mixes. In addition, it would have been helpful to assess the interrater reliability of the variable "absence of potential source of fever".

This is a stage IV clinical decision rule. A stage 4 rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. A stage IV rule requires further validation before it can be applied clinically

AUTHOR'S CONCLUSION: "In summary, we developed a clinical prediction model to aid in identifying febrile girls younger than 2 years who are at risk for urinary tract infection. The model has excellent sensitivity, although further work is necessary to validate the results in different patient populations. When sensitivity is of paramount importance, we recommend obtaining urine culture if any 2 or more of the 5 risk factors are present. Such a strategy leads to identification of 95% of affected children and elimination of the need for a substantial proportion of unnecessary tests. We are currently conducting a formal economic analysis to compare the cost-effectiveness of various screening strategies for urinary tract infection in febrile young children."

POTENTIAL IMPACT: This was a well-designed derivation of a clinical decision rule that identified a high proportion of febrile females with a urinary tract infection and has the potential to decreased the proportion of urinary catheterizations by 30%. The rule requires further validation and particularly in populations with different ethnic mixes before in can be applied clinically.

SEE ALSO: VALIDATION STUDY

Gorelick MH, Hoberman A, Kearney D, Wald E, Shaw KN.
Validation of a Clinical Decision Rule Identifying Febrile Young Girls at High Risk for Urinary Tract Infection.
Pediatr Emerg Care. 2003 Jun;19(3):162-4., PubMed ID: 12813300

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

URINARY TRACT INFECTION: DISPOSITION AND REVISITS

In children less than two year of age presenting to the emergency department with a urinary tract infection what is the association between hospital admission rate and 3-day emergency department revisit requiring admission for those managed as outpatients?

Mariju Baluyot, MD, Laura Papadimitropoulos, MD

April 2019

Chaudhari PP, Monuteaux MC, Bachur RG.

MANAGEMENT OF URINARY TRACT INFECTIONS IN YOUNG CHILDREN: BALANCING ADMISSION WITH THE RISK OF EMERGENCY DEPARTMENT REVISITS.

Academic Pediatrics. 2019 Mar;19(2):203-208.

PubMed ID: 29864523

STUDY DEFINITIONS	
POPULATION	Inclusion: Children aged < 2 years, diagnosis of UTI (ICD codes for UTI, cystitis, and pyelonephritis) Exclusion: Urologic abnormalities (identified by having had visit with primary diagnosis UTI in 12 months before index visit) Chronic comorbidities (as defined by Feudtner et al.) Hospitals excluded if <85% of patients with UTI diagnosis had urine culture sent Patients admitted with primary diagnosis of UTI but did not receive antibiotics Setting: Pediatric Health Information System (PHIS): Administrative Database 48 tertiary US pediatric medical centers (n=36 post inclusion/exclusion applied) ED encounters 1/1/2010 to 12/31/2016.
EXPOSURE	Hospitals with HIGH initial admission rate from the ED (analyzed as continuous)
NO EXPOSURE	Hospital with LOW initial admission rate from the ED (analyzed as continuous)
OUTCOME	Primary Outcome: Association between hospital admission rate and 3 days ED revisit Stratified by age: < 2 months, 2-24 months 1. Discharged patient's 3-day ED revisit rate 2. Discharged patient's 3-day ED revisit requiring admission rate Revisit defined as patient discharged from index visit with subsequent ED visit within 3 days with diagnosis of UTI Effective Admission Rate: Patients admitted initially + Patients discharged with a revisit with admission within 3 days of index visit Secondary Outcome: Trends in admission rate and revisit rate over study period.
DESIGN	Observational: Retrospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Was the sample of patients in a study representative?	Yes. There were 41,792 healthy children aged <2 years with UTI were included in the study. Most children (94%) were classified as having an urban residence, which is consistent with patients who live near most pediatric tertiary care centers. 69% were female and the median age was 6.6 months.
Were the patients classified into prognostically similar groups?	Not applicable
Was follow-up sufficiently complete?	Follow-up was complete for purposes of the data analysis as 3-day ED revisits were measured. However, there was no follow-up regarding for the admitted patients or actual long-term prognosis for patients with UTI. There also may likely be missing data from the database and patients who were not captured in the study which may account for some discrepancies seen in admission rates vs. ED revisit dates.
Were study outcome criteria objective and unbiased?	Yes. Outcome criteria compared hospital admission rate and revisit rate requiring admission with antibiotics

WHAT ARE THE RESULTS?

HOW LIKELY ARE THE OUTCOMES OVER TIME?

N = 41,792 (36 hospitals)
69% Female, median age 6.6 months (IQR 3.0,
Hospital Admission rates: 6%-64%.

DISPOSITION: STRATIFIED BY AGE

	< 2 months	2-24 months	0-24 months
Admission at first visit	89% (6,173/6,968)	15% (5,093/34,824)	27% (11,266/41,792)
D/C + ED revisit	10.1% (80/791)	3.9% (1,156/29,585)	4.1% (1,236/30,526)
D/C + ED revisit + Admit	6.7% (53/791)	1.0% (303/29,585)	1.2% (356/30,526)

DISPOSITION RATE TRENDS (2010-2016)

Age	Admission[1]	ED Revisit[1]	ED Revisit + Admit[1]	Effective Admission[2]
< 2	↓ -4.3% (-7.5,-1.6%) 0.92 (0.95, 1.04)	↑ 8.4% (0.3,16.5%) 1.22 (1.12, 1.32)	↑ 4.0% (-3.6, 11.7%) 1.21 (1.08, 1.37)	↓ -3.4% (-6.0,-0.7%) 0.94 (0.90, 0.98)
2-24	↔ -0.1% (-1.5,1.2%) 0.99 (0.95,1.04)	↔ -0.3% (-1.2,0.5%) 0.98, (0.94,1.03)	↑ 0.5%, (-0.1,1.0%) 1.09 (1.02, 1.16)	↔ 0.2% (-1.2, 1.7%) 0.94 (0.90, 0.98)

1. % change (95% CI), adjusted Odds ratio (95% CI)
2. Patients admitted initially + Patients discharged with a revisit with admission within 3 days
↑ = Increased, ↓ = Decreased, ↔ = Remained Stable

Primary Outcome: Association Between Hospital Admission Rate and Revisit within 3 Days (figure 1). Admission rates and 3-day ED revisit rates were inversely related. For every 1% increase in hospital admission rate, there was -0.07%, 95% CI (-0.13, -0.02) decrease in revisit rate. Hospitals at the 25th percentile had an admission rate of 19.8 ± 1% and a revisit rate of 3.2%. Hospitals at the 75th percentile had an admission rate of 39.4 ± 1% and a revisit rate of 2.0%.

ASSOCIATION BETWEEN ADMISSION AND REVISIT RATES: BY AGE SUBGROUPS

Age	Revisit Rate (Adjusted Odds Ratio (95% CI))	Revisit with Admission Rate (Adjusted Odds Ratio (95% CI))
< 2 months	-0.26, (-0.35, -0.17)	-0.33 (-0.51, -0.15)
2-24 months	-0.06 (-0.12, 0.01)	0.00 (-0.05, 0.05)
0-24 months	-0.07, (-0.13, -0.02)	-0.02, (-0.07, 0.03)

GREEN = Statistically Significant, RED = Not Statistically Significant

HOW PRECISE ARE THE ESTIMATES OF LIKELIHOOD?

See confidence intervals above. The large sample size generally resulted in narrow confidence intervals

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients and their management similar to those in my practice?	Yes. We frequently see children of all ages that we diagnose with UTI in the Emergency Department who we must decide whether we admit vs discharge home on antibiotics.
Was the follow-up sufficiently long?	Yes. For management of simple UTI, follow-up at three days is a reasonable amount of time to estimate effectiveness of outpatient treatment.
Can I use the results in the management of patients in my practice?	These results support the effectiveness of treating UTIs in most young children as an outpatient.

CLINICAL BOTTOM LINE

BACKGROUND: Urinary tract infection is a common diagnosis in the pediatric population. In 1999, a study demonstrated that was no differences in both short- and long-term outcomes in children less than 24 months of age with UTI managed as inpatients compared to outpatients (Hoberman, Pediatrics 1999, PubMed ID: 10390264). This study also demonstrated that 60% of febrile infants with UTI have evidence of pyelonephritis on renal scans.

While most pediatric patients can be treated effectively with oral antibiotics, children younger than 2 years old are often admitted for treatment. The purpose of this study is to explore the risks and benefits of admission for these patients versus outpatient treatment and discharge from the Emergency Department.

CLINICAL QUESTION: In children less than two year of age presenting to the emergency department with urinary tract infection what is the association between hospital admission rate and 3-day emergency department revisit requiring admission for those managed as outpatients?

DESIGN/RISK OF BIAS: This study was a multicenter retrospective analysis completed using information from the Pediatric Health Information System administrative database, which involves 48 tertiary pediatric medical centers in the United States. Data was obtained for ED encounters between 1/1/2010 and 12/31/2016. The retrospective nature of the data does not allow us to determine the reason for the revisit or indications for admission. Revisits to other than the index hospital would not have been included in the analysis.

PRIMARY RESULTS: The analysis included 41,792 children less than 24 months of age with urinary tract infection seen at 36 pediatric hospitals emergency departments. Age was stratified as infants younger than 2 months old and children aged 2-24 months.

Infants younger than 2 months were admitted more frequently for UTI when compared to children aged 2-24 months, 89% vs 15%. Of the children who were discharged, 10.1% of infants younger than 2 months returned to the ED with the same complaint within 3 days, and 6.7% were subsequently admitted. For children aged 2-24 months, 3.9% were seen in the ED within 3 days and 1% were subsequently admitted.

DISPOSITION: STRATIFIED BY AGE			
	< 2 months	2-24 months	0-24 months
Admission at first visit	89% (6,173/6,968)	15% (5,093/34,824)	27% (11,266/41,792)
D/C + ED revisit	10.1% (80/791)	3.9% (1,156/29,585)	4.1% (1,236/30,526)
D/C + ED revisit + Admit	6.7% (53/791)	1.0% (303/29,585)	1.2% (356/30,526)

The researchers also analyzed these outcomes over time (2010 to 2016). They found that infants younger than 2 months had decreased admission rates but increased ED revisits within 3 days, both with and without subsequent admission. Children aged 2-24 months had stable admission rates and ED revisit rates within 3 days, however ED revisit rates within 3 days with subsequent admission increased over this time period.

Admission rates and 3-day ED revisit rates were inversely related. Hospitals with lower admission rates had higher revisit rate but not higher rates of revisits requiring admission. For infants younger than 2 months, there was an association with hospital-level admission rate and ED revisit within 3 days, with and without subsequent admission. There was no association for children aged 2-24 months.

ASSOCIATION BETWEEN ADMISSION AND REVISIT RATES: BY AGE SUBGROUPS		
Age	Revisit Rate (Adjusted Odds Ratio (95% CI))	Revisit with Admission Rate (Adjusted Odds Ratio (95% CI))
< 2 months	-0.26, (-0.35, -0.17)	-0.33 (-0.51, -0.15)
2-24 months	-0.06 (-0.12, 0.01)	0.00 (-0.05, 0.05)
0-24 months	-0.07, (-0.13, -0.02)	-0.02, (-0.07, 0.03)
GREEN = Statistically Significant, RED = Not Statistically Significant		

APPLICABILITY: Given the setting of 36 children's hospital ED's and the inclusion of over 41,000 patients the study's results are likely applicable to pediatric patients seen in the emergency department who are diagnosed with UTI.

AUTHOR'S CONCLUSION: "Substantial variation in admission rates exists for infants and children aged <2 years with a UTI. Although hospitals with lower admission rates at the index visit had higher ED revisit rates among children initially managed on an outpatient basis, those hospitals did not have an increase in revisits leading to hospitalization among young children aged 2-24 months, supporting the effectiveness of outpatient treatment for most pediatric UTIs, particularly in children aged >2 months. Further exploration of patient- and hospital-level factors in admissions and revisits are needed to better inform clinical decisions regarding hospitalization versus outpatient management for young children with UTIs."

POTENTIAL IMPACT: While further prognostic studies may be warranted, this analysis supports the management of uncomplicated UTIs in the young pediatric population in the outpatient setting rather than routine admission, as has been the practice in the past.

URINARY TRACT INFECTION: RISK CALCULATOR DERIVATION

In febrile children less than two years of age, can a clinical prediction model identify those at high risk of UTI in whom to obtain a urinalysis and urine culture and in those who are high risk by clinical parameters does a laboratory prediction model based on urinalysis findings identify those requiring empiric treatment with antibiotics pending urine culture results?

Michael Mojica, MD
June 2018

Shaikh N, Hoberman A, Hum SW, Alberty A, Muniz G, Kurs-Lasky M, Landsittel D, Shope T.

DEVELOPMENT AND VALIDATION OF A CALCULATOR FOR ESTIMATING THE PROBABILITY OF URINARY TRACT INFECTION IN YOUNG FEBRILE CHILDREN.

JAMA Pediatr. 2018 Jun 1;172(6):550-556.
PubMed ID: 29710324

STUDY DEFINITIONS	
POPULATION	Inclusion: Febrile (≥ 38 C) children less than 2 years of age, a single urinalysis and urine culture obtained within 3 hours of each other by bladder catheterization Case: All patients in a retrospective cohort with a UTI Controls: A random sample from a retrospective cohort without a UTI Exclusion: Known abnormalities of the urinary tract (e.g., spina bifida, neurogenic bladder). When > 1 eligible visit during the study period, 1 was randomly selected Specimens collected by a urine bag Setting: Single Children's Hospital Emergency Department (U.S.) Training (Derivation) cohort: 1/2007-4/2013 Independent (Validation) cohort: 7/2015-12/2016
RULE PARAMETERS	Multivariable logistic regression models 1. Clinical model: High risk factors: Age < 12 months, non-black race, female or uncircumcised male, temperature ≥ 39 C (102.2 F) and no other fever source No other fever source: Signs and or symptoms within 24 hours of the ED visit of: acute otitis media, upper respiratory tract infection (any cough or congestion), gastroenteritis, pneumonia, meningitis, bronchiolitis, viral syndrome). 2. Laboratory Models: a. Dipstick: Clinical model + Leukocyte esterase and Nitrite values b. Dipstick + Gram stain mode: Clinical model + Dipstick model + gram stain c. Hemocytometer model: Clinical model + Dipstick model + WBC/microliter d. Enhanced urinalysis model: Clinical + Hemocytometer + gram stain Clinical model (pretest probability of UTI) ≥ 2% = Urine testing indicated Laboratory model (posttest probability of UTI) ≥ 5% = Antibiotics indicated
REFERENCE STANDARD	UTI defined as pyuria (WBC ≥ 5/HPF or WBC ≥ 10/microliter) OR any leukocyte esterase positive AND growth of ≥ 50,000 CFU/ml of a uropathogen
OUTCOME	Model: Area under the receiver operating characteristic curve Model cutoff values: Sensitivity, Specificity (Assumed minimum sensitivity of 95% Note: Test characteristics for the laboratory models apply only to those who are high risk by the clinical model Model performance compared to AAP UTI Guideline algorithm
DESIGN	Nested Case-control study

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. The models included variables identified in previous studies as predictors of UTI (see supplement). Abdominal tenderness, diarrhea, vomiting, and foul-smelling urine were not added because adding them did not improve the model significantly. Duration of fever and history of UTI were dropped from the clinical model because dropping them decreased the predictive ability only marginally.
Were all important predictors present in significant proportion of the study population?	No. The proportion of each of the significant predictors in the cohort was not presented.
Were the outcome event and predictors clearly defined?	Yes. The majority of the clinical and laboratory predictors were objective findings. The only clinical variable open to interpretation was “no other source of fever’ which was clearly defined (see supplement).
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Unclear. This was a retrospective chart review. Likely predictors and outcome variables were collected simultaneously. However, since both the predictors and outcomes are objective, the lack of blinding should not bias their interpretation.
Was the sample size adequate (including an adequate number of outcome events)?	Yes. In general, for logistic regression it is recommended that there be 10 cases for each predictor included in the model. The enhanced urinalysis model had the greatest number of predictors with 9 variables. A 9 variable model would require 90 patients with a UTI and the derivation cohort included 542 patients with a UTI.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SENSITIVITY AND PREDICTIVE VALUE OF A NEGATIVE RULE WITH 95% CONFIDENCE INTERVALS)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SPECIFICITY AND PREDICTIVE VALUE OF A POSITIVE RULE WITH 95% CONFIDENCE INTERVALS)

Training (derivation) cohort: n=1,686 (72.9% 2-11 months, 72.1% female, 69.2% white)
Independent (validation) cohort: n=384 (60.2% 2-11 months, 75.8% female, 52.1% white)

MODEL TEST CHARACTERISTICS

Model	Derivation AUC (95% CI)	Validation AUC (95% CI)	Derivation		Validation	
			SN	SP	SN	SP
Clinical	0.80 (0.77, 0.82)	0.81 (0.72, 0.89)	95%	35%	100%	34%
Dipstick	0.97 (0.96, 0.98)	0.99 (0.98, >0.99)	95%	92%	96%	95%
Dipstick + Gram Stain	0.98 (0.97, 0.99)	0.99 (0.98, >0.99)	96%	92%	100%	92%
Hemocytometer	0.97 (0.96, 0.98)	0.99 (0.98, >0.99)	93%	91%	100%	95%
Enhance UA	0.98 (0.98, 0.99)	0.99 (0.98, >0.99)	96%	93%	96%	93%

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

The UTICalc model was tested in a hypothetical cohort of 1,000 febrile children less than 2 years of age with a 7% UTI rate. Compared to the AAP UTI algorithm, UTICalc would reduce the need for urine sampling by 8.1%, 95% CI (4.2, 12.0%) and reduce the number of missed patients from 3 to 0. It would have been helpful to present the impact on urine sampling and antibiotic use of the models on the entire derivation cohort.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

A separate validation cohort of 384 patients at the same institution was included.
Derivation and validation cohorts had similar test characteristics (see table above)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (See Appendix)	☐ I ☐ II ☐ III ■ IV This a stage IV decision rule. The rule was derived and a separate retrospective cohort was used to validate the model at the same study center. Further external and preferable prospective validation is required before the rule can be applied clinically.
Does the rule make clinical sense?	Yes. The parameters in the clinical and laboratory rule are those factors that we use to inform clinical decision. An enhance urinalysis (using hemocytometer cell count and gram stain performed on uncentrifuged urine) is not universally available. A number of factors typically included in clinical decision making are not present in the models (e.g. pyuria on a standard UA and a past medical history of a UTI). The authors state that they were not independent predictors in their models. It is interesting that pyuria was part of the requirement for the study outcome of UTI but not included in the laboratory models.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Inter-rater reliability of the predictors was not assessed though all but one predictor is an objective clinical or laboratory finding. Only 1 clinical variable, “no other fever source” was potentially subjective and that variable was clearly defined. On the calculator web site this variable is accompanied by a clear description of what is considered another source of fever.
Is the rule applicable to the patients in my practice?	This was a single center study with a predominantly white population. A “nonblack race” is one of the factors in the clinical model indicative of high risk. Prior data has demonstrated that white race indicates a high risk of UTI. It is unclear if this is true of Hispanic or Asian. The prevalence of UTI in the derivation cohort was 32.1% because of the ratio of 1:2 case to controls selected by the authors. The prevalence of the UTI in the validation cohort was 7.8% which is similar to that typically reported in the pediatric UTI literature.
Will the rule results change my management strategy?	Use of the calculator would certainly simplify clinical decision making. Use of the rule assumes that the user agree agrees with a 2% risk of UTI as an indication to obtain a urine sample and a 5% risk as an indication to initiate empiric antibiotics pending culture results.
What are the benefits of applying the rule to my patients?	The benefit of the utilizing the calculator is to target those at highest risk of UTI to avoid unnecessary urine testing and antibiotic therapy ideally without increasing the number missed UTIs.
What are the risks of applying the rule to my patients?	Use of the calculator would require 10 children to undergo catherization for every one child with a UTI (number needed to test = 9.8)

CLINICAL BOTTOM LINE

BACKGROUND: Urinary tract infection is the most common occult infection in febrile children less than 2 years of age occurring in approximately 7%. Approximately 60% of febrile children in this age category will have evidence of pyelonephritis on renal scan. In febrile neonates, UTI is the common reason for both bacteremia and meningitis. Many clinical factors can influence the pretest probability of UTI and inform the decision to obtain a urine specimen. In addition, many of the components of a urinalysis can be used determine the posttest probability of UTI in order to determine who requires empiric antibiotics pending the results of urine culture. This study aims to develop a calculator to answer these two clinical questions. WEB LINK: UTI CALCULATOR

CLINICAL QUESTION: In febrile children less than two years of age, can a clinical prediction model identify those at high risk of UTI in whom to obtain a urinalysis and urine culture and in those who are high risk by clinical parameters does a laboratory prediction model based on urinalysis findings identify those requiring empiric treatment with antibiotics pending urine culture results?

DESIGN/RISK OF BIAS: The was a well-designed, nest case-control study conducted at a single children's hospital ED. Febrile (≥ 38 C) children less than 2 years of age who had a single urinalysis and urine culture obtained within 3 hours of each other by bladder catheterization were included. The study utilized two cohorts of patients to separately derive and validate a UTI risk calculator. The study derived 5 models using logistic regression (1 clinical, 4 laboratory). The models were derived with the assumptions that a 2% risk of UTI is an indication to obtain a urine sample and a 5% risk of UTI is an indication to initiate antibiotic therapy. In deriving the model cutoffs, it was also assumed that clinicians would prefer a minimum sensitivity of 95%.

UTI RISK PREDICTION MODELS

Model	Clinical Parameters*	LE and Nitrite Values	Gram Stain	WBC/microliter
Clinical	X			
Dipstick	X	X		
Dipstick + Gram Stain	X	X	X	
Hemocytometer	X	X		X
Enhance UA	X	X	X	X

*Age < 12 months, non-black race, female or uncircumcised male, temperature ≥ 39 C (102.2 F) and no other fever source

Clinical factors identified as high risk or UTI included an age < 12 months, temperature ≥ 39 C (102.2 F) non-black race, female or uncircumcised male, and no other fever source. "No other fever source" was defined as signs and/or symptoms within 24 hours of the ED visit that could include acute otitis media, upper respiratory tract infection (any cough or congestion) gastroenteritis, pneumonia, meningitis, bronchiolitis, viral syndrome.

PRIMARY RESULTS: The vast majority of patients in both the derivation and validation cohort were 2-11 months of age, female and white. Because of nested case-control design and the selected 1:2 ratio of cases to controls, the prevalence of UTI and predictive values cannot be calculated for from the derivation cohort.

The accuracy of the model as a whole (area under the ROC curve (AUC)) and the sensitivity and specificity at derived model cutoffs are presented below for the derivation and validation cohorts. The clinical model alone had the lowest AUC and a significantly lower specificity than any of the laboratory models. However, it had a 95% sensitivity in identifying those with a UTI risk of greater than 2%. Each of the laboratory models (which include the clinical model) had a higher area AUC, equivalent sensitivities and higher specificities than the clinical model alone.

MODEL TEST CHARACTERISTICS

Model	Derivation AUC (95% CI)	Validation AUC (95% CI)	Derivation		Validation	
			SN	SP	SN	SP
Clinical	0.80 (0.77, 0.82)	0.81 (0.72, 0.89)	95%	35%	100%	34%
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Hemocytometer	0.97 (0.96, 0.98)	0.99 (0.98, >0.99)	93%	91%	100%	95%
Enhance UA	0.98 (0.98, 0.99)	0.99 (0.98, >0.99)	96%	93%	96%	93%

The UTICalc model was tested in a hypothetical cohort of 1,000 febrile children less than 2 years of age with a 7% UTI rate. Compared to the AAP UTI algorithm, UTICalc would reduce the need for urine sampling by 8.1%, 95% CI (4.2, 12.0%) and reduce the number of missed patients from 3 to 0. It would have been helpful to present the impact of use of the models on the entire derivation cohort on the rate of urine sampling and antibiotic use.

APPLICABILITY: This was a retrospective cohort of febrile children less than 2 years of age at a single children's hospital ED who had urine specimen obtained by bladder catherization. Indication for who required urine testing was not specified. Their population may represent a high-risk population to start. Because of the selection of a 1:2 ratio of cases to controls, a true prevalence of UTI could not be determined from the derivation cohort. However, the prevalence of the UTI in the validation cohort was 7.8% which is similar to that typically reported in the pediatric UTI literature. The study's results are likely generalizable to patients 2-11 months of age who were female and white who made up the majority of the study population. A "nonblack race" is one of the factors in the clinical model indicative of high risk. Prior data has demonstrated that being of white race indicates a high risk of UTI. It is unclear if the higher UTI risk is the same for Hispanic, Asian or other races as well. 70% of the patients in the derivation cohort were white. This is likely similar to our NYU population but certainly not true of our Bellevue population

Utilization of the calculator requires that the use agree with the authors selection of a pretest probability of ≥ 2% for testing and posttest probability of ≥ 5% for treatment established by the authors.

The retrospective data collection did not allow for the assessment of inter-rater reliability of the clinical predictor "no other fever source". This is only potentially subjective variable. On the calculator web site this variable is accompanied by a clear description of what is considered another source of fever.

This a stage IV decision rule. The rule was derived and a separate retrospective cohort was used to validate the model at the same study center. Further validation is required before the rule can be applied clinically.

AUTHOR'S CONCLUSION: "Accurate diagnosis of UTI is important to reduce the delay in diagnosis and to avoid unnecessary treatment with antimicrobial drugs. The approach advocated here tailors testing and treatment to the risk factors present in the child being assessed, thus offering the potential to improve outcomes for children with UTI."

POTENTIAL IMPACT: The authors derived and internally validated clinical and laboratory models of the risk of UTI which simplify the process of deciding which febrile children require urine testing and which require antibiotics based on urine testing. The laboratory models (which included the clinical model) had high accuracy, sensitivity and specificity. Compared to the AAP UTI algorithm, UTICalc could potentially reduce the need for urine sampling and reduce the number of missed UTI's. This a level 4 clinical decision rule that would benefit from prospective, external validation. WEB LINK: UTI CALCULATOR

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

URINARY TRACT INFECTION: OUTPATIENT MANAGEMENT

In children 1 to 24 months with fever and a gram negative urinary tract infection is treatment with outpatient oral antibiotics when compared to inpatient intravenous antibiotics (followed by outpatient oral antibiotics) as effective in both short term (sterilization of urine and time to defervescence) and long term (incidence of reinfection and incidence and extent of renal scarring at 6 months) clinical outcomes?

Katrina Knapp D.O., Debbie Levine M.D.
September 2016

Hoberman A, Wald ER, Hickey RW, Baskin M, Charron M, Majd M, Kearney DH, Reynolds EA, Ruley J, Janosky JE.

ORAL VERSUS INITIAL INTRAVENOUS THERAPY FOR URINARY TRACT INFECTIONS IN YOUNG FEBRILE CHILDREN.

Pediatrics. 1999 Jul;104(1 Pt 1):79-86.
PubMed ID: 10390264

STUDY DEFINITIONS	
POPULATION	Inclusion: 1 to 24 months of age, rectal temperature > 38.3C (at presentation or within 24 hours), suspected UTI (pyuria (>10 WBC/mm^3) and bacteriuria (>1 Gram (-) rod per 10 oil immersion fields) and a catheterized urine culture (> 50,000 CFU, single pathogen) Exclusion: 1. Negative urine culture 2. Cephalosporin hypersensitivity 3. Gram (+) positive cocci in the urine 4. Unequivocal alternative source of fever 5. History of UTI/GU tract abnormalities 6. Systemic antibiotics within 48 hours 7. Underlying chronic disease. 8. Appeared severely ill: e.g. systolic BP < 60 mmHg, or cap refill > 3 seconds Setting: Multicenter, 4 Children's Hospital, 1/92-7/97
INTERVENTION	Cefixime for 14 days. D#1: 16mg/kg PO x 1 (in ED), then D#2-14: 8 mg/kg/day Admission to the hospital: 4-8 weeks of age
CONTROL	Cefotaxime (200 mg/kg/day divided Q6H) for 3 days or until child was afebrile for 24 hours then Cefixime (8 mg/kg once daily) to complete a 14-day course. Admission to the hospital: All
CO-INTERVENTIONS	Prophylaxis: Treatment followed by 2-weeks Cefixime (4 mg/kg daily) until VCUG Follow up visit: 24 hours, 2 weeks, Repeat UCxs, 24 hours, 3 months, 6 months and any time febrile Phone follow up: Days 2, 10. Compliance: Cefixime urine assay at 2 weeks Imaging: Renal scan at entry & 6 months, VCUG 4-5 weeks, renal ultrasound 6 months
OUTCOME	Short Term Outcomes: Sterilization of urine at 24 hours Time to defervescence Long Term Morbidity: Incidence of reinfection Incidence and extent of renal scarring on Tm-DMSA scan at 6 months
DESIGN	Interventional: Randomized clinical trial

ARE THE RESULTS VALID?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. subjects randomized at each site and stratified based on age (1-12, 13-24 months) and duration of fever (<, ≥ 48 hours)
Was randomization concealed?	Unclear. The procedure for allocating patients to treatment groups after randomization was not provided.
Were patients in the study groups similar with respect to known prognostic factors?	Yes (Table 1). No significant difference between distributions of demographic, clinical, or laboratory characteristics between the oral therapy group or the initial IV therapy group. (Table 2), Higher incidence of acute pyelonephritis in oral antibiotic group (65.3%) compared to initial IV antibiotic group (56.9%). Although not statistically significant this could have potentially biased the results in favor of intravenous antibiotics.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The patients, parents, and treating physicians knew what group the patient was assigned too. The short-term outcome measures were objective (fever, and urine cultures) so it seems that the study not being blinded could not really effect the interpretation of the outcome. Renal scans were interpreted independently by two investigators who were unaware of treatment assignments.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDY'S CONCLUSION?	
Was follow-up complete?	The extent that follow up was complete was dependent on the specific short and long term outcomes.

LOST TO FOLLOW UP	ORAL ANTIBIOTICS N =153	IV ANTIBIOTICS N = 153
Defervescence	0 (0%)	0 (0%)
Urine Culture @ 24 hours	Total in both groups = 15 (5%)	
Incidence of reinfection	13 (8.5%)	6 (3.9%)
VCUG at 4-5 weeks	4 (2.6%)	3 (1.96%)
Renal Scan at 6 months	21 (13.7%)	13 (8.5%)

Were patients analyzed in the groups to which they were randomized?	Yes. An intention to treat analysis performed. 1 patient who was allocated to the oral antibiotic group vomited and crossed over to the intravenous antibiotic group.
Was the trial stopped early?	No, the trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Demographics
306 patients (PO: 153, IV: 153)
61% acute pyelonephritis (APN) on initial renal scan
Higher WBC, CRP, ESR in those with APN
97% E. Coli. 0.3% resistant to Cefixime.
4% bacteremic: Younger, longer duration of fever, higher acute phase reactants.
All repeat blood cultures negative @ 24 hours

Short Term: Urine culture @ 24hours: All sterile
Short Term: Time to defervescence: 23 hours in both groups

LONG TERM: REINFECTION IN 6 MONTHS

	REINFECTION		
	YES	NO	
ORAL ANTIBIOTICS	8	132	140
INTRAVENOUS ANTIBIOTICS	13	134	147
	21	266	287

Absolute Risk: PO Antibiotics group: 8/140 = 5.7%
Absolute Risk: IV Antibiotics group: 13/147 = 8.8%
Absolute Risk Difference: 8.8% - 5.7% = 3.1%, 95% CI (-3.2, 9.5%)
Absolute Risk: PO Antibiotics group: 15/132 = 11.4%
Absolute Risk: IV Antibiotics group: 11/140 = 7.8%
Absolute Risk Difference = 7.8% - 11.4 % = - 3.6%, 95% CI (-10.9, 3.6%)

LONG TERM: RENAL SCARRING AT 6 MONTHS

	REINFECTION		
	YES	NO	
ORAL ANTIBIOTICS	15	117	132
INTRAVENOUS ANTIBIOTICS	11	129	140
	26	246	272

Extent of Renal Scarring: No difference
Compliance: Cefixime in urine in 85% (no difference)
Confidence intervals not provided (calculated at CEBM Web Site: LINK)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Reinfection: Risk Difference: 3.1%, 95% CI (-3.2, 9.5%)
Renal Scarring: Risk Difference: -3.5%, 95% CI (-10.9, 3.6%)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. The patient population was similar to our patient population. Majority were female and very few were circumcised (3% circumcised).
Were all clinically important outcomes considered?	Yes. All clinically important outcomes were considered. Short term, long term and economic outcomes included. Long term significance of renal scarring is unknown.
Are the likely treatment benefits worth the potential harm and costs?	Benefits of outpatient antibiotics include: less disruption in family function, less nosocomial infections. Cost of treatment between groups: Total cost of oral therapy for 20 patients: $ 3,630. Total cost of IV therapy for 20 patients: $7,382

CLINICAL BOTTOM LINE

BACKGROUND: At the time this study was conducted management of young children with a febrile urinary tract infection included admission for intravenous antibiotics.

CLINICAL QUESTION: In children 1 to 24 months with fever and a gram negative urinary tract infection is treatment with outpatient oral antibiotics when compared to inpatient intravenous antibiotics (followed by outpatient oral antibiotics) as effective in both short term (sterilization of urine and time to defervescence) and long term (incidence of reinfection and incidence and extent of renal scarring at 6 months) clinical outcomes?

DESIGN/VALIDITY: This was a randomized clinical trial that included 306 patients in the primary analysis. Patients were randomized to a two-week course of either oral antibiotics (Outpatient Cefixime) or initial intravenous antibiotics (Inpatient Ceftriaxone until afebrile then outpatient Cefixime). 2 weeks of prophylactic Cefixime was administered until a voiding cystourethrogram was performed.

This was a well-designed study with minimal risk of bias. The study was not blinded. However, the outcomes included could not be influenced by knowledge of the treatment group. The use of oral antibiotics for 2 weeks' post treatment could have resulted in fewer reinfections though this should not have affected the proportion of reinfection in each treatment group. Only 11% of study patients that did not follow up for the 6-month renal scan.

PRIMARY RESULT: All patients who had repeat urine cultures 24 hours after starting antibiotics had negative urine cultures. Time to defervescence was essentially identical (PO 23.2 vs IV 23.3 hours). Regarding long-term outcomes; the absolute risk of renal scarring at 6 months on DMSA renal scan was 11.4% for the oral antibiotic group and 7.8% for the initial IV antibiotic group. The absolute risk difference was 3.5%, 95% CI (-10.9, 3.6%). There was also no difference between the extent of scarring. The absolute risk of reinfections was 5.7% in the oral antibiotic and 8.8% in the intravenous antibiotics group. The absolute risk difference was 3.1%, 95% CI (-3.2, 9.5%).

It is important to note that when we treat febrile urinary tract infections in this age group, we are primarily treating pyelonephritis. 61% of patients had evidence of acute pyelonephritis on initial DMSA renal scan performed within 48 hours of study entry. Those with acute pyelonephritis had higher levels of acute phase reactants (WBC, ESR, CRP). 4% of children with UTI were bacteremic. These patients tended to be younger, have a longer duration of fever before initiation of antibiotics and have higher levels of acute phase reactants. All repeat blood cultures were negative within 24 hours. The authors question the utility of obtaining blood cultures and repeat urine cultures in those with febrile urinary tract infections.

APPLICABILITY: This was a broad population and the results of this study are likely generalizable to those who do not meet exclusion criteria. Less than 0.5% of patients were 4-7 weeks of age and the proportion of patients less than 3 months of age could not be determined from the data presented. These younger patients were also the those who were more likely to be bacteremic so caution should be taken with this ago group and close follow up is essential. The rate of E. Coli Cefixime resistance at the time of the study was less than 0.5%. The appropriateness of Cefixime as an antibiotic choice will be determined by current, local resistance rates.

AUTHORS CONCLUSION: “As we study the long-term effects (if any) of small renal scars, outpatient management of young children with fever and UTI with oral Cefixime can be recommended as a safe and effective treatment that will result in substantial reductions of health care expenditures. Aggressive surveillance for infection of the urinary tract in young febrile children leads to early diagnosis and excellent outcome with either oral or IV therapy with third-generation Cephalosporins.”

POTENTIAL IMPACT: This study has changed the way we manage febrile infants with a urinary tract infection and emphasized that the majority of these children have pyelonephritis and not cystitis. There was limited data on the youngest infants and they were the groups with the highest rate of bacteremia. Antibiotic selection should be guided by local bacteriology and resistance patterns. The ability to tolerate oral antibiotics should be assessed and close follow up be arranged.

HEAD AND NECK INFECTIONS

1. Conjunctivitis: Topical Antibiotic Selection: J Ped 2013
2. Croup: Dexamethasone Mild Croup: N Engl J Med. 2004
3. Croup: Corticosteroid Selection: Arch Dis Child. 2006
4. Otitis Media: ABx for Tympanostomy: N Engl J Med. 2014
5. Otitis Media: Augmentin vs Placebo: N Engl J Med. 2011
6. Otitis Media: Treatment Duration: N Engl J Med. 2016
7. Otitis Media: Treat Duration (Meta-Analysis) JAMA 1998
8. Sinusitis: Augmentin vs Placebo: Pediatrics 2009
9. URI: Cold Medications: Pediatrics 2004
10. URI: Combining Antipyretics: BMJ 2008

CONJUNCTIVITIS: TOPICAL ANTIBIOTIC SELECTION

In children with acute bacterial conjunctivitis, does Polymyxin B/Trimethoprim (Polytrim) when compared to Moxifloxacin (Vigamox) result in equivalent or better rates of clinical and bacteriologic cure?

Alvira Shah M.D., Debbie Levine M.D.
September 3, 2013

Williams L, Malhotra Y, Murante B, Laverty S, Cook S, Topa D, Hardy D, Wang H, Gigliotti F.

A SINGLE-BLINDED RANDOMIZED CLINICAL TRIAL COMPARING POLYMYXIN-B-TRIMETHOPRIM AND MOXIFLOXACIN FOR TREATMENT OF ACUTE CONJUNCTIVITIS IN CHILDREN.

J Pediatr. 2013 Apr;162(4):857-61.
PubMed ID: 23092529

STUDY DEFINITIONS	
POPULATION	Inclusion: Clinical diagnosis of conjunctivitis. Presence of lid edema, conjunctival erythema, eye discharge, and/or subconjunctival hemorrhage Exclusion: History of allergies, foreign body or eye trauma. Antibiotics in past week. Non-English speaking patients Setting: Children's hospital ambulatory clinic and suburban pediatric practice. Fall 2007-2010
INTERVENTION	Polymyxin B-trimethoprim (Polytrim): 4 times a day for 7 days
CONTROL	Moxifloxacin (Vigamox): 3 times a day for 7 days
CO-INTERVENTIONS	Patients were given the study medications (did not need to fill a prescription) Follow-up phone call at 4-6 days: Assess clinical response. Returned for a follow-up visit at day 7-10: Assessment of physical findings, follow-up conjunctival culture
OUTCOME	Clinical Cure: Complete resolution of all signs and symptoms of conjunctivitis Bacteriologic Cure: 7-10 days
DESIGN	Interventional: Randomized clinical trial

ARE THE RESULTS VALID?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Using randomization tables were assigned in a 1:1 ratio
Was randomization concealed?	Yes. Patients received brown paper bags with either antibiotic. Study personnel were unaware of which medication each patient received. Patients had written directions for each antibiotic (Moxifloxacin TID and Polytrim QID) and were told not to tell study personnel which medication they had been assigned.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. The two groups were found to be similar at enrollment. (See Table pg. 859) Both groups are similar with respect to mean age, signs, symptoms and organisms recovered.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded	The study was single blinded. Study personnel did not know what antibiotic group the patient was allocated to. The patients/parents were aware of which group they were allocated to but it does not seem than knowledge of group assignment could bias the study outcomes of clinical cure and bacteriologic cure at 4-6.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	No. 89 out of 120 total enrolled patients (approximately 25%) were not available for clinical follow up on day 7-10. Figure 1 and Figure 2 indicate that the group size in both antibiotic groups remained roughly equal at 7-10 days.
Were patients analyzed in the groups to which they were randomized?	Yes. An intention to treat analysis was not specifically stated though it does not appear that there could be crossover between the groups
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Clinical Cure by phone follow up on days 4-6.
Clinical Cure and Bacteriologic Cure on clinical follow up visit and days 7-10

	CLINICAL CURE (4-6 days)		
	YES	NO	
MOXIFLOXACIN	43	13	56
POLYMYXIN/TMP	42	16	59

Absolute Risk (*no cure)*: Moxifloxacin = 13/56 = 23%
Absolute Risk (*no cure)*: Polymyxin/TMP = 16/58 = 28%
Absolute Risk Difference (M – P/T) = 23 - 28% = - 5%
(P-value = 0.04, therefore we reject the null hypothesis that Moxifloxacin is superior, and accept the alternative hypothesis that Polymyxin/TMP is non-inferior to Moxifloxacin)

Relative Risk (no cure) - M/(P/T) = (13/56)/(16/58) = 0.23/0.28 = 0.82

	Polymyxin/TMP	Moxifloxacin
Clinical Cure (4-6 days)	72%	77%
Clinical Cure (7-10 days)	96%	95%
Bacterial Cure (7-10 days)	61%	79%

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Precision alludes to confidence intervals. Absolute risk difference = - 5% 90% CI (-20 to 11%) Since 0 is included in this CI there was no statistically significant difference between the two antibiotics.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	The patients were recruited from a hospital clinic and suburban practice so they may be similar to patients at Bellevue and Tisch. However non-English speaking patients were excluded which would be a large proportion of our patients. It is not clear how these patient's compliance would compare to our patients. We could assume there would be non-compliance issues as it is difficult to get eye drops into a child several times a day. Compliance with the medication regimens was not measured for this study.
Were all clinically important outcomes considered?	No. They assessed resolution of symptoms, which is the most important outcome. They also looked at bacteriological cure. They could also have measured days missed from daycare/school/work. No later follow up was done to measure recurrence (given the fact that bacterial cure averaged only 70%) and did not measure transfer of illness to close contacts.
Are the likely treatment benefits worth the potential harm and costs?	Yes. In this study no serious adverse outcomes were reported though rare adverse events could not be excluded. The authors note that using Polymyxin B/TMP rather than Moxifloxacin could decrease costs (~$300 million/year). For patients without insurance, it is important to consider that Polytrim is significantly cheaper (~ 20 x less on average) than Moxifloxacin. Even with insurance, it may not cover Moxifloxacin.

CLINICAL BOTTOM LINE

BACKGROUND: Conjunctivitis is a very common condition. In children, bacterial conjunctivitis is the most common etiology (55-68%). Responsible organisms are those found in both acute otitis media and sinusitis (Strep pneumonia, H influenzae (non-typable) and Moraxella catarrhalis). While generally self-limited, antibiotics have been shown to accelerate clinical cure and microbiologic clearance. It has been suggested that topical Fluoroquinolones are better for treating conjunctivitis than older medications due to increasing antibiotic resistance of pathogens and because Moxifloxacin has a lower minimum inhibitory concentration (MIC). However, the relationship between MIC and clinical response to topical antibiotics remains undefined.

CLINICAL QUESTION: In children with acute bacterial conjunctivitis, does the Polymyxin B/ Trimethoprim (Polytrim) when compared to Moxifloxacin (Vigamox) result in equivalent or better rates of clinical and bacteriologic cure?

DESIGN/VALIDITY: This study was a prospective, single blinded, randomized clinical trial enrolling 114 patients in the primary analysis. This was a well-designed study with a few validity concerns. Investigators defined conjunctivitis by the clinical findings of lid edema, conjunctival erythema or subconjunctival hemorrhage or eye discharge or crusting open awakening. Clinical cure was defined as resolution of all signs and symptoms of conjunctivitis. Compliance with the medication regimen was not measured. Polymixin B/Trimethoprim was given 4 times a day as compared to 3 times a day for Moxifloxacin. Poorer compliance in the Polymixin B/Trimethoprim group would favor the efficacy of Moxifloxacin. In addition, 25% of the patients were not available for the 7-10 day follow up. This is likely related to the early resolution of symptoms.

PRIMARY OUTCOME: 65% of the initial cultures grew bacterial pathogens. After 4-6 days of treatment, 77% of Moxifloxacin group and 72% of Polymixin B/Trimethoprim group were clinically cured as per parental report. After 7-10 days, clinical cure was observed in 95% of the Moxifloxacin group and 96% of the Polymixin B/Trimethoprim group. Clinical cure rates did not differ at days 4-6 or 7-10. The authors conclude that Polymyxin B/Trimethoprim was non-inferior to Moxifloxacin. The authors estimate that the use of Polymyxin B /Trimethoprim could save as much as $300 million a year. Adverse events such as pain with administration, recurrence of conjunctivitis or spread of illness to contacts were not reported. Bacteriologic cure rates were higher though not statistically significant in the moxifloxacin group (79%) compared to Polymyxin B-trimethoprim (61%). This does not correlate with more rapid resolution of conjunctivitis.

APPLICABILITY: The results of this study appear applicable to pediatric patients with conjunctivitis in general. The results are particularly relevant to patients who do not have medical insurance.

AUTHOR'S CONCLUSIONS: "Polymyxin B-trimethoprim continues to be an effective treatment for acute conjunctivitis with a clinical response rate that does not differ from moxifloxacin. Use of Polymyxin B-trimethoprim for the treatment of conjunctivitis would result in significant cost savings compared with fluoroquinolones."

POTENTIAL IMPACT: Given the equivalent efficacy and cost savings it appears reasonable to initiate treatment with Polymixin B/Trimethoprim in the pediatric patient with uncomplicated conjunctivitis.

CROUP:
DEXAMETHASONE FOR MILD CROUP

In children with mild croup does oral Dexamethasone when compared to Placebo reduce the risk of unscheduled return visits for medical care?

Ramona Warren M.D., Michael Mojica, M.D.
November 2004

Bjornson CL, Klassen TP, Williamson J, Brant R, Mitton C, Plint A, Bulloch B, Evered L, Johnson DW;
Pediatric Emergency Research Canada Network.

A RANDOMIZED TRIAL OF A SINGLE DOSE OF ORAL DEXAMETHASONE FOR MILD CROUP

N Engl J Med. 2004 Sep 23;351(13):1306-13.
PubMed ID: 15385657

STUDY DEFINITIONS	
POPULATION	Inclusion: Mild croup (onset within 72 hours of a seal-like, barking cough) and a Westley croup score of ≤ 2 of 17 points. Exclusion: Other cause of stridor (epiglottitis, bacterial tracheitis, supraglottic foreign body), history of congenital or acquired stridor, chronic pulmonary disease, asthma, severe systemic disease, exposure to varicella within 21 days, known immune dysfunction; corticosteroids within prior 2 weeks, treatment with Epinephrine before enrollment, inability of parent to speak English or French; lack of a telephone in the home, prior visit to an emergency department for the same episode of croup. Setting: 4 Children's Hospital EDs, 2 seasons: 9/2001-4/2002 and 9/2002-2/2003
INTERVENTION	Dexamethasone: 0.6 mg/kg PO, maximum 20 mg. (Observed for 30 minutes. If vomiting occurred, one additional dose was given)
CONTROL	Placebo of similar volume, appearance, smell and taste
OUTCOME	Primary: Return to a health care provider for croup within 7 days Secondary: Presence of ongoing croup symptoms days 1, 2 and 3 (seal-like barking cough or stridor in past 24 hours) Economic analysis Hours of child sleep missed Degree of parental stress Adverse events
DESIGN	Interventional: Randomized clinical trial

ARE THE RESULTS VALID?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized in computer-generated random permuted blocks of 6 to 10 patients.
Was randomization concealed?	Yes. Codes for medication and placebo were kept locked in the pharmacy until after data was collected. It does not appear that there was an opportunity to bias allocation though the authors did not specifically state the allocation was concealed
Were patients in the study groups similar with respect to known prognostic factors?	Yes, the experimental and control groups were assessed prior to treatment and were similar in their baseline health and current medical state (Table 2). A logistic regression analysis attempting to stratify for possible differences in baseline characteristics revealed similar results to the primary analysis.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Investigators, clinical personnel and parents were blinded to the study group. Dexamethasone and placebo looked alike and the identity of the medications were coded.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. 5/358 (1.4%) in the Dexamethasone group and 7/359 (1.9%) of the Placebo patients were lost to follow up.
Were patients analyzed in the groups to which they were randomized?	Yes. An intention to treat analysis included all enrolled patients for which data was available. A worse case scenario sensitivity analysis was also performed with the assumption that all Dexamethasone treated children with missing outcome data were considered to return for care while all Placebo treated children were not.
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Primary Outcome: Return visit within 7 days

	RETURN VISIT		
	YES	NO	
DEXAMETHASONE	26	328	354
PLACEBO	54	300	354

Risk of Return Visit (Dexamethasone): 26/354 = 7.3 %
Risk of Return Visit (Placebo): 54/354 = 15.3%
Risk Difference (Placebo – Dexamethasone) = 15.3- 7.3 = 8%, 95% CI (3.3, 12.5%)

Relative Risk (Dexamethasone/Placebo) = 7.3/15.3 = 0.48, 95% CI (0.31, 0.75%)
Relative Risk (Placebo/Dexamethasone) = 15.3/7.3 = 2.1

Secondary Outcomes:

Ongoing symptoms: First 24 hours odds ratio 3.2 (1.5-6.8) but was equalized by day 3.

Economic cost: Savings of $21/case with Dexamethasone.

Hours of sleep lost:
2.9 +/- 3.8 hours in the Dexamethasone group
4.2 +/- 4.7 hours in the placebo group ($p < 0.001$).

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

ARD = 8%, 95% CI (3.3, 12.5%)
RR = 0.48, 95% CI (0.31, 0.75%)
The study had 80% power to detect a 5.7% difference in the primary outcome, return to care within 7 days. The absolute risk difference (ARD) of 8% is greater than the 5.7% difference the authors considered a clinically significant difference. The adjusted odds ratio (Placebo/Dex) in the regression analysis was 2.4 (1.4-3.9.) This is similar to the relative risk (Placebo/Dex) of 2.1 reported in the primary analysis

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. Inclusion/exclusion criteria and patient characteristics appear similar to our ED population
Were all clinically important outcomes considered?	The difficulty with the primary outcome is that it is unclear if those that returned to care were indeed sicker. Approximately 50% of return visits required additional therapy and 2.5% required admission. A subgroup analysis of those requiring additional treatment or admission on revisit would have been helpful
Are the likely treatment benefits worth the potential harm and costs?	Yes. NNT = 1/(ARD) = 1/(0.08) = 12. The number needed to treat indicates that for every 12 patients treated with Dexamethasone there will be 1 less return visit compared to those treated with Placebo. There were no significant adverse events though this study was not powered to address rare adverse events. Adoption of a treatment strategy that includes Dexamethasone in a larger population may reveal adverse events not identified in this study.

CLINICAL BOTTOM LINE

BACKGROUND: The literature supports the use of corticosteroids in moderate-severe croup. Intramuscular dexamethasone has traditionally been used though more recent studies suggest that orally administered corticosteroids are effective as well. This study was designed to address the efficacy of corticosteroids in the patient with mild croup.

CLINICAL QUESTION: In children with mild croup does oral Dexamethasone when compared to Placebo reduce the risk of unscheduled returns for medical care?

DESIGN/VALIDITY: This was a well-designed randomized clinical trial that included 708 patients with mild croup in the primary intention to treat analysis. There were no major validity concerns with the studies design. The difficulty with the primary outcome of unscheduled return visit is that it is often not clear why patients return. In this study, approximately 50% of return visits required additional therapy and 2.5% required admission.

PRIMARY RESULTS: A single dose of oral Dexamethasone (0.6 mg/kg, maximum 20 mg) in children with mild croup (defined as a croup score ≤ 2) resulted in a decrease in return visits for medical care. Patients who received Dexamethasone were approximately half as likely to return to care. For every patient 12 patients treated dexamethasone one additional unscheduled revisit could be avoided when compared to placebo. Secondary outcome measures (clinical, social and economic) and secondary analysis (sensitivity analysis and logistic regression) support the magnitude and direction of this result. No significant adverse events were attributed to Dexamethasone though the study was not powered to identify rare events.

APPLICABILITY: The results appear applicable to the majority of patients with mild croup that would fit the authors inclusion and exclusion criteria.

AUTHOR'S CONCLUSION: "Our study shows small but important benefits of dexamethasone treatment for children with mild croup. The findings are consistent across a range of clinical, social, and economic outcome measures. Oral dexamethasone therapy is simple, inexpensive, and effective. Therefore, although the long-term effects are not known, we advocate dexamethasone. treatment for essentially all children with croup.

POTENTIAL IMPACT: A single oral dose of Dexamethasone for patients with mild group demonstrated substantial benefit in unscheduled return visits with little apparent risk.

CROUP:
CORTICOSTEROID SELECTION

In patients with mild to moderate croup, is a single oral dose of Prednisolone (1 mg/kg) equally as effective as a single oral dose of Dexamethasone (0.15 mg/kg) in reducing unscheduled return visits for symptoms related to croup?

Karen Franco, M.D., Michael Mojica, M.D.
June 2006

Sparrow A, Geelhoed G.

PREDNISOLONE VS DEXAMETHASONE IN CROUP: A RANDOMIZED EQUIVALENCE TRIAL.

Arch Dis Child. 2006 Jul;91(7):580-3.
PubMed ID: 16624882

STUDY DEFINITIONS	
POPULATION	Inclusion: > 3 months, have not received steroids, mild to moderate croup (Defined by the modified Taussig Croup Score (See Appendix)) Exclusion: Families without a telephone, limited knowledge of English Setting: Single Children's Hospital ED (Australia), 7/2001-10/2001
INTERVENTION	Dexamethasone: 0.15 mg/kg PO (same volume, similar taste, appearance).
CONTROL	Prednisolone: 1 mg/kg PO
CO-INTERVENTIONS	Repeated observations Q30 minutes after administration; Q1 hour for next 4 hours and Q4 hours until discharge. Nebulized adrenaline as clinically indicated Discharge criteria: Minimal stridor or chest wall retractions (Croup score 0 or 1) Phone follow up at 7-10 days: Revisit for croup symptoms, admission, duration of the ‘‘barking cough’’ and viral symptoms (fever, rhinorrhea)
OUTCOME	Primary Outcome: Unscheduled re-attendance to medical care. Secondary Outcomes: Length of stay in ED, use of nebulized epinephrine
DESIGN	Interventional: Randomized clinical trial (Equivalence hypothesis)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized in computer generated blocks of 10.
Was randomization concealed?	Yes. The pharmacy concealed randomization by labeling study medications with A or B. Samples could not be differentiated and the same amount of volume given. Unblinding occurred only after follow-up was complete.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Table 1 shows patients in both groups had similar initial croup scores. The Prednisolone group was about 8 months older. The Dexamethasone group had a longer duration of symptoms, potentially closer to recovery. These differences, however, were not statistically significantly.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Unclear. Not specifically stated
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. 133 patients were enrolled and follow up was available for all 133.
Were patients analyzed in the groups to which they were randomized?	Yes. This was an intention to treat analysis. All patients were accounted for in the analysis. It is not reported if any of the patients vomited the study medication.
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 33, Dexamethasone: 68, Prednisolone: 65

Primary Outcome: Need for Medical Revisit
Dexamethasone: 5/68 (7%)
Prednisolone: 19/65 (29%)
Absolute Risk Difference: 29–7% = 22%, 95%CI (8, 35%)
This confidence interval is the outside 0-7.5% range of equivalence specified by the authors indicating that Prednisolone is not equivalent to Dexamethasone

Secondary Outcomes:
No difference in the time spent in the emergency department, use of adrenaline, duration of croup symptoms, or viral symptoms.
No adverse events were noted

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The 95% confidence for the risk difference is presented. The lower limit of 8% is very close to the 7.5% the authors proposed as the upper limit for equivalence.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Yes. Patients were similar regarding age to our population. It is unclear if there are differences that should be considered in the Australian croup population. The typical dose of Dexamethasone used in our ED is 0.6 mg/kg which is 4 times the study's dose.
Were all patient important outcomes considered?	Yes. Recurrence or unscheduled medical visit, croup score (croup severity), length of ED visit, duration of symptoms, epinephrine use. Unscheduled medical visits is a difficult outcome measure to interpret. The reasons for revisits were not stated. A croup score on revisit and the requirement for additional interventions would have helped to clarify the significance of the revisits
Are the likely treatment benefits worth the potential harm and costs?	No treatment benefit was found. Single dose of oral prednisone was not better than a single dose of oral dexamethasone in mild to moderate croup. We typically administer 1-2 mg/kg of Prednisolone. The sample was too small to make conclusions about rare adverse events.

CLINICAL BOTTOM LINE

BACKGROUND: Corticosteroids have been conclusively shown to be of benefit in patients with mild. moderate and severe croup. Initial studies utilized intramuscular Dexamethasone with more recent trials have demonstrated oral Dexamethasone to be equally efficacious. Intramuscular Dexamethasone is painful while oral Dexamethasone is not always readily available in a dosage form that is tolerated by children. In addition, physicians have considerable experience is dosing pediatric patients with oral Prednisolone or Prednisone. A single dose of either me medication witnessed in the emergency department ensures compliance.

CLINICAL QUESTION: In patients with mild to moderate croup, is a single oral dose of Prednisolone (1 mg/kg) equally as effective as a single oral dose of Dexamethasone (0.15 mg/kg) in reducing unscheduled return visits for symptoms related to croup?

DESIGN/VALIDITY: This was a randomized controlled trial of 133 patients (Dexamethasone: 68, Prednisolone: 65) in the primary intention to treat analysis. This was an equivalence hypothesis comparing a single dose of 0.15 mg/kg of Dexamethasone and 1.0 mg/kg of Prednisolone. The doses were intended to be equivalent. Others would consider a 0.75 mg/kg of Prednisolone equivalent and use of the 1.0 mg/kg dose could potentially bias study's results in favor of Prednisolone. The dose of Dexamethasone used in the study is 25% of the dose that we typically administer. The primary outcome was unscheduled return visits related to persistent or worsening of croup symptoms. Unscheduled medical visits is a difficult outcome measure to interpret. Only 5 of the 24 patients (12%) with a revisit required admission. A croup score on revisit and the requirement for additional interventions would have helped to clarify the significance of the revisits.

PRIMARY RESULTS: In this study, a single equipotent dose of oral prednisone (1 mg/kg) was not found to be equivalent to a single dose of oral dexamethasone (0.15 mg.kg) in reducing unscheduled revisits in patients with mild to moderate croup. Absolute Risk Difference: Dexamethasone 7% - Prednisolone 29%, = 22% 95%CI (8, 35%). This confidence interval is the outside 0-7.5% range of equivalence specified by the authors indicating that Prednisolone is not equivalent to Dexamethasone.

APPLICABILITY: The study's results can likely be generalized to patients meeting the study's inclusion and exclusion criteria.

AUTHOR'S CONCLUSION: "A single oral dose of prednisolone is less effective than a single oral dose of dexamethasone in reducing unscheduled re-presentation to medical care in children with mild to moderate croup."

POTENTIAL IMPACT: The study's findings of nonequivalence is consistent with the longer half-life of Dexamethasone. Further study is required to determine if a two-dose regimen of Prednisolone or a higher dose single dose may be equivalent to a single dose of oral dexamethasone.

APPENDIX: CROUP SCORE

MODIFIED TAUSSIG CROUP SCORE		
STRIDOR	None	0
	Only on crying, exertion	1
	At rest	2
	Severe (biphasic)	3
RETRACTIONS	None	0
	Only on crying, exertion	1
	At rest	2
	Severe (biphasic)	3
Mild: 1-3, Moderate: 3-4, Severe: 5-6		

ACUTE OTITIS MEDIA:
ANTIBIOTIC DURATION (META-ANALYSIS)

In children with acute otitis media will a shorter course of antibiotics when compared to a longer course of antibiotics result in more treatment failures?

Michael Mojica, M.D.
October 2016

Kozyrskyj AL, Hildes-Ripstein GE, Longstaffe SE, Wincott JL, Sitar DS, Klassen TP, Moffatt ME.

TREATMENT OF ACUTE OTITIS MEDIA WITH A SHORTENED COURSE OF ANTIBIOTICS: A META ANALYSIS

JAMA. 1998 Jun 3;279(21):1736-42.
PubMed ID: 10796591

STUDY DEFINITIONS	
POPULATION	Inclusion: Clinical trials, 4weeks-18 years, clinical diagnosis of acute otitis media, no antibiotics at time of diagnosis, random assignment, study groups of < 7or > 7 days of treatment, assessment of clinical resolution Exclusion: Surgical co-intervention e.g. tympanocentesis Setting: Not presented for individual studies. Included 19 studies published 1982-1997
INTERVENTION	Short acting antibiotics: A. Penicillin, Amoxicillin, Cefaclor, Cefuroxime, Cefpodoxime, Cefprozil <7d B. Azithromycin for 3-5 days C. Ceftriaxone (intramuscular) x 1 dose
CONTROL	Long acting antibiotics: A. Penicillin VK, Amoxicillin, Cefaclor, Cefuroxime, Cefixime, Cefprozil for 7-10 days. Compared to same antibiotic (12/17), different antibiotic (12/17) B. Amoxicillin, Cefaclor, Clarithromycin for 10 days C. Amoxicillin, Cefaclor, Trimethoprim-Sulfamethoxazole for 7-10 days
OUTCOMES	Primary Outcome: Treatment failure 1. Lack of clinical resolution: signs and symptoms not improved or resolved 2. Relapse or recurrence within 31 days Secondary Outcomes: 1. Number of treatment failures 2. Relapses 3. Recurrences within 1-3 months
DESIGN	Systematic review and meta-analysis of randomized clinical trials

HOW SERIOUS IS THE RISK OF BIAS?	
Did the review include explicitly and appropriate eligibility criteria?	Yes. The question was focused with regard to patient population and outcome. The intervention of short course of antibiotics was divided into three groups (Table 1). There was great variability in the antibiotics in the first group and variability in the controls in the ceftriaxone and azithromycin group. Studies as old as 16 years prior to the publication date were included that utilize antibiotics no longer recommended for acute otitis media as epidemiology due to new vaccines and resistance patterns have evolved. Many trials did not compare the same antibiotic as both the long and short duration treatment. Though adverse events were reported in the results, no mention of definitions or which data was abstracted was made in the methods. Study settings not presented.
Was biased selection and reporting of studies unlikely?	Yes. The inclusion criteria were appropriate to the study question and were applied prospectively. Databases search included: Medline, EMBase, Current contents and Science Citation Index. Reference lists of included studies were searched. Search criteria were well defined and not limited by language. There was no mention of attempts at correspondence with authors/experts or the pharmaceutical industry to identify missed/unpublished studies. The funnel plot (Figure 2) indicates that publication bias was unlikely though a statistical analysis for publication bias (e.g. Begg's Test) was not presented.
Were the primary studies of high methodologic quality?	Yes. The Jadad criteria for RCT's were used to assess validity. The mean Jadad score was 2.66 (≤ 2 is generally considered poor). The sensitivity analysis addresses some of the validity concerns (lack of concealment, low validity studies). There was no difference in the primary outcome when low quality studies or those with lack of concealment were excluded.
Were assessment of studies reproducible?	Yes. Seven blinded investigators independently assessed both the study selection and study quality. The inter-rater reliability was excellent for study inclusion (kappa 0.89, 95% CI (0.86-0.92)) and study quality (kappa 0.82, 95% CI (0.79-0.85)).

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

Yes. Figure 1 is a Forrest plot of the individual studies of the short acting antibiotic group broken down by time of assessment of outcome. There appears to be reasonable overlap of the confidence intervals in each of the groups. The investigators state that statistical heterogeneity was assessed but do not provide the results of either a chi squared or I^2 test. Forrest plots for the Ceftriaxone and Azithromycin Groups were not provided.

WHAT ARE THE OVERALL RESULTS OF THE REVIEW? Note: We have not included the results of the Azithromycin or Ceftriaxone subgroups in this review.

Primary Outcome: Treatment Failure (5-day course/8-10 days course) at 20-30 days
Odds Ratio = Treatment Failure Short / Long Course
Absolute Risk Difference = Short Course – Long Course

	ODDS RATIO (95%CI)	RISK DIFFERENCE (95%CI)
8-30 days	1.38 (1.15,1.66)*	
8-19 days	1.52 (1.17,1.98)*	7.8% (4,11.6%)*
20-30 days	1.22 (0.98,1.54)	2.3% (-0.2,4.9%)
*Significant increase in treatment failure with short course		

Odds Ratio at 30-40 days and 90 days similar to 20-30 days

Secondary Outcomes:
No difference in failure, relapse or recurrences within 30 days

Subgroup Analysis (30 days)
< 2 years, Odds Ratio: 0.71, 95% CI (0.3, 0.64), Sig, n=118
≥ 2 years, Odds Ratio: 1.01, 95% CI (0.53, 1.94), NS, n=235
Perforated, Odds Ratio: 3.62, 95% CI (0.8, 16.1), NS, n=27
Not perforated, Odds Ratio: 1.06, 95% CI (0.4, 2.75), NS, n=101

Sensitivity Analysis (Table 2)
No difference in treatment failure at 20-30 day for high vs low quality studies, adequate vs inadequate concealment and chronic otitis media included or excluded.
Improved counted as failure Odds Ratio: 1.24 (1.01,1.54), sig
Same antibiotic in both arms Odds Ratio: 1.25 (0.90,1.74), NS

HOW PRECISE WERE THE RESULTS?

Confidence intervals presented above

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were all patient-important outcomes considered?	Unclear. Adverse events were reported but no criteria for abstraction from the original studies were presented. Compliance and infectious complication (e.g. mastoiditis) would be additional outcomes we would use to make clinical decisions on duration of therapy
Are any postulated subgroup effects credible?	Subgroups analyzed include: > or > 2 years and perforated vs not perforated. Those with a perforation had a higher risk of treatment failure at 30 days (OR 3.62 (0.81,16.06)) though this difference was not statistically significant. This is likely due to the small sample size (n = 27). This makes clinical sense.
What is the overall quality of the evidence?	Poor. The antibiotic intervention was poorly defined including a wide variety of antibiotics over a long period of time. Essentially combining apples and oranges
Are the benefits worth the costs and potential risks?	Unclear. First, we don't know for certain what the benefits would be of specific antibiotics. Second, we don't know the potential harms. There is a potential benefit to society in decreasing the emergence of resistance bacteria. 44 patients would need to be treated with a long course of antibiotics compared to a short course to prevent one additional treatment failure at 20-30 days.

CLINICAL BOTTOM LINE

BACKGROUND: A shorter antibiotic course for acute otitis media could improve compliance and potentially reduce the emergence of resistant bacteria. The 2013 American Academy of Pediatrics Acute Otitis Media practice guideline makes the following recommendations for duration of therapy:
10-day Course: Children < 2 years of age and all children with severe symptoms.
7-day Course: Children 2 to 5 years of age with mild or moderate acute otitis media.
5-7 day Course: Children ≥ 6 years and older with mild to moderate symptoms.

CLINICAL QUESTION: In children with acute otitis media will a shorter course of antibiotics when compared to a longer course of antibiotics result in more treatment failures?

DESIGN/VALIDITY: This was a systematic review and meta-analysis. The study was well designed but suffered from a major validity concern. Studies as old as 16 years prior to the publication date were included that utilized antibiotics no longer recommended for acute otitis media as epidemiology due to new vaccines and resistance patterns have evolved. Many trials did not compare the same antibiotic as both the long and short duration treatment. It is very difficult to draw conclusion from this trials results based on these concerns.

PRIMARY RESULTS: The study demonstrated no difference in treatment failure at 20-30 days between a short course (< 5 days) and long course (7-10 days) of antibiotics. Odds ratio (Short/Long) = 1.22 95% CI (0.98, 1.54). However, there was a significant increase in treatment failure with a short course of antibiotics when measured at 8-30 Days: OR 1.38, 95% CI (1.15,1.66) and at 8-19 Days: OR 1.52, 95% CI (1.17,1.98). In the sensitivity analysis of trials that utilized the same antibiotic in both arms there was no statically significant difference in treatment failure with a short course of antibiotics at 8-30 days ((OR 1.54, 95% CI (1.21-1.95)) or at 20-30 days ((OR 1.25, 95% CI (0.90,1.74)).

APPLICABILITY: The applicability of the study's results is limited by the risks of bias discussed previously. While the articles may have met criteria a meta-analysis from a heterogeneity stand point they should not have been combined from a methodological standpoint. Compliance with the antibiotic regimen was not measure. The study was not powered to identify rare complications of otitis media such a mastoiditis

AUTHORS CONCLUSIONS: "The meta-analysis results support the use of 5 days of a short-acting antibiotic in uncomplicated AOM in the event that clinicians and parents decide to use antibiotics. Treatment with a shortened course of antibiotics has the potential to greatly reduce antibiotic use in regions where 10 days of treatment is considered the standard, with anticipated cost savings, improved compliance, and decreased antibiotic resistance."

POTENTIAL IMPACT: Changes in the epidemiology of acute otitis media due to new vaccines and an increase in bacterial resistance make the application of this studies results difficult. It does not appear that the articles included in the meta-analysis should have been combined from a methodological standpoint. A short course of one antibiotic should not be compared to a long course of a difference antibiotic. The authors emphasize in the abstract and their conclusions that a short course of antibiotics was comparable in terms of treatment failure at 20-30 days. However, there was a statistically significant increase in treatment failures in the short course of antibiotics group when analyzed at 8-19 days and 8-30 days. This study does not represent the level of evidence required to change current practice

ACUTE OTITIS MEDIA: AUGMENTIN VS PLACEBO

Among children 6 to 23 months with acute otitis media, does Amoxicillin/Clavulanate when compared to Placebo result in less symptom burden and clinical failures?

Kelly Cleary, M.D., Dennis Heon, M.D.
February 2011

Hoberman A, Paradise JL, Rockette HE, Shaikh N, Wald ER, Kearney DH, Colborn DK, Kurs-Lasky M, Bhatnagar S, Haralam MA, Zoffel LM, Jenkins C, Pope MA, Balentine TL, Barbadora KA.

TREATMENT OF ACUTE OTITIS MEDIA IN CHILDREN UNDER 2 YEARS OF AGE.

N Engl J Med. 2011 Jan 13;364(2):105-15.
PubMed ID: 21226576

STUDY DEFINITIONS	
POPULATION	Inclusion: Children with ≥ doses of pneumococcal conjugate vaccine, acute otitis media onset in past 48 hours, parents rated symptoms with a score of at least 3 on the Acute Otitis Media Severity of Symptoms (AOM-SOS) scale (See Appendix), presence of middle-ear effusion, moderate or marked bulging of the tympanic membrane or slight bulging with otalgia or marked erythema of the membrane Exclusion: Acute illness (e.g., pneumonia), chronic illness (e.g., cystic fibrosis), allergy to Amoxicillin, received ≥ 1 dose of antimicrobial within prior 96 hours, otalgia > 48 hours, or perforation of the tympanic membrane Setting: Single Children's hospital and associated private practice, 11/2006-3/2009
INTERVENTION	Augmentin ES = Amoxicillin (90mg/kg) + Clavulanate (6.4 mg/kg) BID x 10 days
CONTROL	Placebo of similar appearance and taste BID x 10 days
OUTCOME	Primary Outcomes: Time to resolution of symptoms: Time to the first recording of an AOM-SOS score of 0 or 1 and the time to the second of two successive recordings of that score. Symptom burden over time: Mean AOM-SOS score each day over the first 7 days and the groups' weighted mean scores for that period. Secondary Outcomes: Overall clinical efficacy Use of acetaminophen Adverse events Nasopharyngeal colonization rates Use of health care resources.
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. They stratified children according to whether they had a history of recurrent AOM (>3 episodes in the preceding 6 months or >4 episodes in past year) and according to their exposure or non-exposure to >3 children for at least 10 hours per week. Then, at each study site within each stratum, children were randomized in blocks of 4 in a 1:1 ratio.
Was randomization concealed?	Yes. The placebo was similar to the drug in appearance and taste.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. The groups were similar with respect to exposure to other children, baseline AOM-SOS, degree of membrane bulging and other measured characteristics (Table 1)
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The parents, research personnel, and the healthcare providers ‘who were not associated with the study’ were blinded to the patient group assignments.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. 96% of the children completed all scheduled study visits.
Were patients analyzed in the groups to which they were randomized?	Yes. The analyses were based on the intention to treat principle.
Was the trial stopped early	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

INITIAL RESOLUTION OF SYMPTOMS				
Day	2	4	7	p = 0.14
Amoxicillin/Clavulanate	35%	61%	80%	
Placebo	28%	54%	74%	
Risk Difference	7%	7%	6%	
Relative Risk	1.25	1.13	1.08	

SUSTAINED RESOLUTION OF SYMPTOMS				
Day	2	4	7	p = 0.04
Amoxicillin/Clavulanate	20%	41%	67%	
Placebo	14%	36%	53%	
Risk Difference	6%	5%	14%	
Relative Risk	1.42	1.14	1.26	

MEAN SYMPTOM BURDEN OVER 1ST 7 DAYS	
Amoxicillin/Clavulanate	2.79 +/- 0.16
Placebo	3.42 +/- 0.19
Mean Difference	0.63, 95% CI (0.15, 1.11)

CLINICAL FAILURE				
	D4-5	D10-12	Severe	Non-Severe
Amoxicillin/Clavulanate	4%	16%	19%	14%
Placebo	23%	51%	61%	43%
Risk Difference	19% (12-27)	35% (25-45)	42%	29%
Number Needed to Treat	5	3	2	3

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence intervals were only provided for some parameters. See above

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Patients were similar in regard to age and disease severity. The ethnicity in our population differs with a lesser percentage of white patients.
Were all patient important outcomes considered?	Yes. All clinically important outcomes were considered. However, the study was not powered to identify rare adverse events such as mastoiditis.
Are the likely treatment benefits worth the potential harm and costs?	The number needed to treat for initial resolution of symptoms is 14. (NNT = 1/ARD = 1/0.07). The article does not focus on the adverse effects of antibiotic administration though it mentions that diarrhea and diaper dermatitis were common among children who received Augmentin.

CLINICAL BOTTOM LINE

BACKGROUND: Otitis media is the most common indication for antibiotics in children. A strategy of "watchful waiting" in which children with acute otitis media are not immediately treated with antibiotic therapy, has been endorsed by the American Academy of Pediatrics as an option in children over two years of age with non-severe disease. The studies on which this recommendation has been based have been criticized for lack of stringent diagnostic criteria, small sample sizes and use of antibiotics in suboptimal doses. This randomized clinical trial attempts to determine the extent that antibiotic treatment affects the course of both signs and symptoms of acute otitis media.

CLINICAL QUESTION: Among children 6 to 23 months with acute otitis media, does Augmentin when compared to Placebo result in less symptom burden and clinical failures?

DESIGN/VALIDITY: This is a well-designed randomized trial of 291 patients who received amoxicillin clavulanate or placebo for 10 days. There were no major validity concerns

PRIMARY RESULTS: The primary outcomes were based on the acute otitis media symptom severity score (AOM-SOS). The study found a statistically significant benefit of Augmentin when compared to placebo in the sustained resolution of symptoms on days 2, 4, 7 and mean AOM-SOS over time. Although the mean AOM-SOS scores showed a statistically significant difference, it is unclear that this difference is clinically significance as well. The study also demonstrated a significant reduction in clinical failures with Augmentin. The article showed its most promising results in the subgroup of those with severe AOM. Those treated with antimicrobial therapy had an absolute risk reduction in clinical failure of 42%. Only 2 children with severe disease would need to be treated with Augmentin to prevent one additional clinical failure compared to placebo. The results were nearly as good in those with non-severe disease.

AUTHOR'S CONCLUSION: "In conclusion, among children 6 to 23 months of age with acute otitis media, treatment with amoxicillin–clavulanate for 10 days affords a measurable short-term benefit, irrespective of the apparent severity of the illness. The benefit must be weighed against concern not only about the side effects of the medication but also about the contribution of antimicrobial treatment to the emergence of bacterial resistance. These considerations underscore the need to restrict treatment to children whose illness is diagnosed with the use of stringent criteria."

POTENTIAL IMPACT: As the epidemiology of acute otitis media changes so must our approach. With the use of the 2 pneumococcal vaccines the prevalence of acute otitis media due to Streptococcus pneumoniae has declined. Some recent studies have shown non-typable Haemophillus influenzae to be the most common organism. Both non-typable Haemophillus influenzae and Moraxella catarrhalis have high rates of beta lactamase activity. Increasing the dose of Amoxicillin may improve coverage of streptococcus pneumoniae but does not help to overcome resistance due to beta lactamase positivity. Studies that have demonstrated that Amoxicillin is as effective as placebo may just be demonstrating that an ineffective antibiotic is equivalent to placebo. In patients who meet diagnostic criteria for acute otitis media an antibiotic that overcomes beta lactamase producing organisms such as Amoxicillin clavulanate or a 2nd or 3rd generation cephalosporin should be considered.

APPENDIX

ACUTE OTITIS MEDIA SEVERITY OF SYMPTOMS SCALE			
	1	2	3
Ear pain	None	A little	A lot
Ear tugging	None	A little	A lot
Irritability	None	A little	A lot
Increased crying	None	A little	A lot
Decreased play	None	A little	A lot
Eating less	None	A little	A lot
Maximum temperature	None	A little	A lot

ACUTE OTITIS MEDIA: TREATMENT DURATION

In children ages 6-23 months of age with a diagnosis of acute otitis media is treatment with Amoxicillin-Clavulanate for 5 days followed by 5 days of Placebo, non-inferior to course of Amoxicillin-Clavulanate for 10 days) in the rate of clinical failure?

Kelsey Fawcett, M.D., Rebecca Burton, M.D.
February 2017

Hoberman A, Paradise JL, Rockette HE, Kearney DH, Bhatnagar S, Shope TR, Martin JM, Kurs-Lasky M, Copelli SJ, Colborn DK, Block SL, Labella JJ, Lynch TG, Cohen NL, Haralam M, Pope MA, Nagg JP, Green MD, Shaikh N.

SHORTENED ANTIMICROBIAL TREATMENT FOR ACUTE OTITIS MEDIA IN YOUNG CHILDREN

N Engl J Med. 2016 Dec 22;375(25):2446-2456.
PubMed ID: 28002709

STUDY DEFINITIONS	
POPULATION	Inclusion: 6-23 months, received ≥ 2 doses of conjugate pneumococcal vaccine, diagnosed with acute otitis media based on 3 criteria: 1. Onset of symptoms within 48 hours (score ≥ 3 on AOM-SOS scale), 2. Presence of middle ear effusion 3. Moderate or marked bulging of the tympanic membrane or slight bulging accompanied by otalgia or erythema. Exclusion: Tympanic membrane perforation Allergy to Amoxicillin ≥ 1 dose of an antimicrobial agent within previous 96 hours. Setting: Children's Hospital affiliated pediatric practices, and a Pediatric and Adult Research Center, 1/2012-9/2015
INTERVENTION	Amoxicillin-Clavulanate (90 mg/kg Amoxicillin, 6.4 mg/kg Clavulanate per day) for 5 days followed by a 5-day course of placebo (Medication was provided)
CONTROL	Amoxicillin-Clavulanate (90 mg/kg Amoxicillin, 6.4 mg/kg Clavulanate per day) for 10 days (Medication was provided). Dosing frequency not provided.
CO-INTERVENTIONS	Study medications provided to patient Acetaminophen as necessary for fever or pain Phone follow-up: Day 4-6 Office visits: End of treatment (day 12-14), Q6 weeks until the end of respiratory season (or September is enrolled at end of respiratory season) Those who treatment failure or > 1 recurrence were treated with either Amoxicillin-Clavulanate, Cefdinir or Ceftriaxone. Those with 1 recurrence after day 16 were treated with the originally assigned regimen
OUTCOME	Primary Outcome: Percentage of children with clinical failure after treatment of the index infection. Clinical failure: 1. Worsening of symptoms or otoscopic signs (e.g. bulging) or 2. Did not have complete/near complete resolution of clinical signs and symptoms attributable to acute otitis media by the end of treatment. Secondary Outcomes: 1. Symptom burden from day 6-14: Daily AOM-SOS (See Appendix) 2. Rates of recurrence: Acute otitis media > 16 days from index episode 3. Outcomes in treating recurrences 4. Total days of antimicrobial treatment 5. Rates of nasopharyngeal colonization 6. Use of other health care services 7. Rates of missed work or special childcare arrangements needed 8. Parental satisfaction with study treatment
DESIGN	Interventional: Randomized clinical trial (non-inferiority hypothesis)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. The patients were randomized. Patients with acute otitis media were stratified into randomized groups by age (6-11 months, 12-17 months, 18-23 months) and by exposure or non-exposure to 3 or more children for 10 or more hours per week.
Was randomization concealed?	Yes. Study packets prepared by investigational pharmacy. The placebo that was used was the same color, odor, texture, and taste as Amoxicillin-Clavulanate. Though not explicitly stated, there did not appear to be an opportunity to bias the allocation process.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. See Table 1. The patient's in the 2 study groups were similar with respect to age, sex, exposure to other children, AOM-SOS score, estimated severity of illness based on pain and fever, the number of ears affected by the infection, and the degree of tympanic membrane bulging associated with their acute otitis media. It is unknown whether the patient's in the study had any other comorbid conditions or if they had a prior history of acute otitis media.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study was blinded. Neither the patient/parents or the treating physician was aware of the treatment the child was receiving.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. End-of-treatment assessments (day 12-14) were done in 93% (238/257) of the patients in the 10-day group and in 89% (229/258) of patients in the 5-day treatment group. End of respiratory season assessments were done in 93% (238/257) of the patients in the 10-day group and in 85% (219/258) of patients in the 5-day treatment group.
Were patients analyzed in the groups to which they were randomized?	Yes. Patients were analyzed in both an intention to treat and per protocol analysis (both excluding those lost to follow-up).
Was the trial stopped early?	Yes. The trial was stopped early when the external data and the safety monitoring board for the study determined that the primary objective of the study had been realized.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 467 (intention to treat analysis)
Severe illness: 55%
Bilateral: 49%
Compliance: 93% 1st 3 days, 89% for ≥ 80% of doses

PRIMARY OUTCOME: CLINICAL FAILURE

INTENTION TO TREAT	CLINICAL FAILURE		
	YES	NO	
10 DAY TREATMENT	39	199	238
5 DAY TREATMENT	77	152	229
	116	351	467

Prevalence: 116/467 = 24.8%
Absolute Risk: 10-days: 39/238 = 16%
Absolute Risk: 5-days: 77/229 = 34%
Absolute Risk Difference: = AR (10-days – 5-days)
= 34% - 16% = 18%, 95% CI (9, 25%).
Relative Risk: = AR 5-day treatment / AR 10-day
= 34%/16% = 2.1, 95% CI (1.5, 2.9)
(Results of the per protocol analysis were similar)

SECONDARY OUTCOMES

	5-day	10-day
Decrease AOM-SOS by 50%*	80%	90%
Residual effusion	65%	62%
Clinical failure in recurrence	28%	19%
Total days antibiotics*	15 ±12	21 ± 13
Nasopharyngeal colonization with penicillin resistant strep pneumoniae	44%	47%
*Statistically significant difference		

Adverse Events: Diarrhea and diaper dermatitis requiring an antifungal occurred equally in the 2 study groups

Percentage of children with recurrence of AOM was greater among those with residual effusion, than those without residual effusion (48% vs 29%, respectively).

No significant difference between use of other health care services, missed work/additional child care needs, or parental satisfaction between the 2 groups.

Two groups combined:
Treatment failures greater in those with bilateral OM (35% vs 15%) and those with exposure to ≥ 3 children for > 10 hours per week (29% vs 19%)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?
Statistical Significance: The confidence intervals for the primary outcomes absolute risk difference and relative risk are moderately wide (imprecise) and indicate a statistically significant difference Clinical Significance: The authors defined non-inferiority as no more than a 10% greater rate of clinical failure in the 5-day treatment group than in the 10-day treatment group. The upper limit of the confidence interval for the risk difference is 25% and is > 10%. In fact, the risk difference is > 10%. Can conclude that a 5-day course is inferior to a 10-day course. Note: A 10-day course was also significantly better (superior) when analyzed using a superiority hypothesis.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. The patients in the study were similar to that of our patient population. The study patients were provided the study medications. Our patients, who receive prescriptions, may have lower rate of compliance. The clinical failure rate of 25% seem somewhat high for patients starting therapy with Augmentin. The study results may not be generalizable to those with otitis media greater than 23 months of age.
Were all patient important outcomes considered?	Yes. Important outcomes were considered in this study including failure of treatment, recurrence of infection requiring additional treatment, and side effects of antibiotic treatment. Patient/Parent outcomes included satisfaction with treatment, rates of missed work or special childcare arrangements needed and need for additional health services
Are the likely treatment benefits worth the potential harm and costs?	A 10-day course was significantly better (superior) when analyzed using a superiority analysis. NNT = 1/ARD = 1/ 0.18 = 5.5. For every 5.5 patients treated with 10 days of Amoxicillin-Clavulanate 1 additional clinical failure would be avoided compared to 5 days of treatment The proposed shortened duration of treatment is not worth the potential harm and costs. This study demonstrated that a shorter course of antibiotics for the treatment of AOM in children under the age of 2 does not result in better outcomes than the traditional duration of therapy. Furthermore, children treated with shorter course of antibiotics were more likely to have residual effusion and recurrent AOM, requiring additional antibiotic therapy.

CLINICAL BOTTOM LINE

BACKGROUND: Acute otitis media is the most commonly diagnosed bacterial illnesses and the most common indication for antibiotics in children under 2 years of age. Current guidelines recommend therapy with high dose Amoxicillin or close observation ("watchful waiting") depending on age, the severity of illness, and laterality (AAP, Pediatrics 2013, PubMed ID: 23439909). A 10-day course of antibiotics is recommended for children less than 2 years of age and any child with severe symptoms. A shorter course could potentially reduce overall antibiotic use and the emergence of antimicrobial resistance.

The studies on which the observation option has been based have been criticized for lack of stringent diagnostic criteria, small sample sizes and use of antibiotics in suboptimal doses. Two well-designed clinical trials (Hoberman, NEJM 2011, PubMed ID: 23439909 and Tähtinen, NEJM 2011, PubMed ID: 212265577) randomized approximately 600 children meeting strict diagnostic criteria for acute otitis media to receive Amoxicillin/Clavulanic acid or placebo. These studies demonstrated a significant reduction in symptom burden and clinical failures in those who received antibiotics. The authors conclude that those patients with a clear diagnosis of acute otitis media would benefit from antibiotic therapy. If the incidence of streptococcal pneumoniae continues to decline due to vaccination, then antibiotics with greater activity against beta lactamase producing gram negative organisms may supplant Amoxicillin as the preferred first-line agent.

CLINICAL QUESTION: In children ages 6-23 months of age with a diagnosis of acute otitis media is treatment with a 5-day course of antibiotics (Amoxicillin-Clavulanate for 5 days followed by 5 days of Placebo) non-inferior to a standard 10-day course of antibiotics (Amoxicillin-Clavulanate for 10 days) in the rate of clinical failure?

STUDY DESIGN/RISK OF BIAS: This study was multi-center, double-blind, randomized control trial. Included 467 patients in intention to treat analysis with a non-inferiority hypothesis. The patients that were included in the study were children under the age of 2 years with a diagnosis of acute otitis media based on 3 criteria: onset of symptoms within the preceding 48 hours with an Acute Otitis Media Severity of Symptoms (AOM-SOS) scale of 3 or more, middle ear effusion, or bulging of the tympanic membrane. Both the patients and the treating physician were blinded to the treatment which consisted of either 5 days of high dose (90 mg/kg/day) Amoxicillin-Clavulanate followed by 5 days of placebo or 10 days of high dose Amoxicillin-Clavulanate.

This was a well-designed study without apparent risk of bias. To reduce the potential for subjectivity in the diagnosis of acute otitis media, participating physicians underwent otoscopic training. In addition, patients were selected based on strict diagnostic criteria. Follow-up occurred frequently and adherence to medication was greater than 80% in both groups. The study did not state whether the patients had co-morbid medical conditions (e.g. cleft palate) or a history of prior episodes of acute otitis media.

PRIMARY OUTCOMES: Patients in the 5-day treatment of Amoxicillin-Clavulanate were 18% more likely to have clinical failure in comparison to those who had been treated for the traditional 10-day course (Absolute Risk Difference: 18%, 95% CI (9, 25%). The authors defined non-inferiority as no more than a 10% higher rate of clinical failure in the 5-day treatment group than in the 10-day treatment group. The upper limit of the confidence interval for the risk difference (25%) is > 10% indicating that a 5-day course is NOT non-inferior to a 10-day course. A 10-day course was significantly better (superior)

when analyzed using a superiority analysis. You would have to treat 5.5 patients with 10 days of Amoxicillin-Clavulanate to prevent 1 additional clinical failure compared to 5 days of treatment (Number needed to treat = 1/ARD = 1/(0.18) = 5.5).

APPLICABILITY: The study's results are likely generalizable to those patients with acute otitis media meeting the study's inclusion and inclusion criteria. Applicability to patients with acute otitis media greater than 23 months of age is unclear.

AUTHORS CONCLUSION: "In conclusion, in the current study involving children 6 to 23 months of age, the treatment of acute otitis media with amoxicillin–clavulanate for 5 days afforded less-favorable short-term outcomes than treatment for 10 days; in addition, neither the rate of adverse events nor the rate of emergence of antimicrobial resistance was lower with the shorter regimen."

POTENTIAL IMPACT: The current recommended treatment of 10-days duration for acute otitis media, seems to be the most effective treatment for children under the age of 2 years. This study demonstrated that 10 days of antibiotic therapy for the treatment of acute otitis media is superior to a shorter (5 days) antibiotic course.

Head to head studies comparing the efficacy and safety of Amoxicillin to Amoxicillin-Clavulanate would help to resolve this question of which agent should be considered first line for acute otitis media.

APPENDIX: AOM-SOS SCORE

ACUTE OTITIS MEDIA SEVERITY OF SYMPTOMS SCALE			
	1	2	3
Ear pain	None	A little	A lot
Ear tugging	None	A little	A lot
Irritability	None	A little	A lot
Increased crying	None	A little	A lot
Decreased play	None	A little	A lot
Eating less	None	A little	A lot
Maximum temperature	None	A little	A lot

ACUTE OTITIS MEDIA: TYMPANOSTOMY TUBE TREATMENT

In children with tympanostomy tubes and an acute onset of otorrhea, what is the effectiveness of topical antibiotics with a corticosteroid when compared to oral antibiotics or a strategy of observation without treatment in reducing treatment failures?

Michael Mojica, M.D.
March 2014

van Dongen TM, van der Heijden GJ, Venekamp RP, Rovers MM, Schilder AG.

A TRIAL OF TREATMENT FOR ACUTE OTORRHEA IN CHILDREN WITH TYMPANOSTOMY TUBES

N Engl J Med. 2014 Feb 20;370(8):723-33.
PubMed: 24552319

STUDY DEFINITIONS	
POPULATION	Inclusion: 1-10 years old, tympanostomy tubes, otorrhea ≤ 7days Exclusion: 1. Temperature > 38.5 (101.3) 2. Antibiotics in prior 2 weeks 3. Tympanostomy tubes placed in prior 2 weeks 4. Otorrhea in prior 4 weeks 5. Otorrhea ≥ 3 episodes in past 6 months 6. Otorrhea ≥ 4 episodes in past 12 months 7. Trisomy 21 8. Craniofacial anomalies 9. Immunodeficiency Setting: Dutch ENT surgeons, general practitioners in outpatient settings. 6/2009-5/2012
INTERVENTION	1. Amoxicillin 30 mg/kg/day and Clavulanate 7.5 mg/kg/day divided TID x 7 days 2. Bacicoline-B (Bacitracin & Colistin & Hydrocortisone) 5 drops TID x 7 days
CONTROL	No treatment
OUTCOME	Primary Outcome: Treatment Failure: Otorrhea in 1 or 2 ears by otoscopy at the 2-week follow up visit. Secondary Outcomes: Duration of otorrhea Median number of days with otorrhea over 6 months Recurrence General and disease specific quality of life Infectious complications Adverse events
DESIGN	Interventional: Randomized clinical trial

ARE THE RESULTS VALID?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. An independent data manager generated a randomization sequence with block sizes of 6 and stratified by age (< 4 years or ≥ 4 years)
Was randomization concealed?	Yes. The randomization assignment was concealed and could not be predicted in advance or during enrollment.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. (Table 1). The oral antibiotic group had a lower percentage of children with tympanostomy tubes due to recurrence of acute otitis media (rather than for persistent otitis media with effusion). If patients with recurrent otitis media had an increased risk of resistant organisms due to a greater exposure to antibiotics then this could have biased the results toward the oral antibiotic group. The regression analysis could account for this difference.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	This was an open label study. Patients, parents and physicians were not blind to the study group assignment. This could potentially effect their interpretation of the outcomes. Data analysis was blinded to study group.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. At two weeks, 228 of the 230 (99%) patients were included in the analysis of the primary outcome.
Were patients analyzed in the groups to which they were randomized?	Yes. The primary analysis was an intention to treat analysis (Figure 1). The intention to treat analysis included 228 of the 230 (99%) patients enrolled. 200 of the 230 (87%) patients received the study interventions as intended per protocol. A per protocol analysis was not reported for comparison.
Was the trial stopped early?	Yes. The study was stopped early. The sample size determination indicated the need to enroll 315 patients for a clinically significant effect size of 20%. 2 years into the trial only 150 patients were enrolled. An unscheduled interim analysis revealed a 30% difference and the study was ended with a total sample size of 230 patients.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Primary Outcome: Treatment Failure (TF) (Table 2)
(N = 228/230 with data available for primary outcome)
Absolute Risk Topical: 4/76 = 5%
Absolute Risk Oral: 34/77 = 44%
Absolute Risk None: 41/77 = 55%

Risk Difference: RD = A-B (95% Confidence Interval)
Risk Difference (Topical – Oral): 5% – 44% = -39%, 95% CI (-51, -26%)
Risk Difference (Topical – None): 5% – 55% = -49%, 955 CI (-62, -37%)
Risk Difference (Oral – None): 44% – 55% = -11%, 95% CI, (-27, 5%)
The authors considered a 20% reduction (risk difference) in treatment failure to be clinically significant

Relative Risk: RR = A/B (95% Confidence Interval)
Relative Risk (Topical/Oral): 5%/44% = 0.12, 95% CI (0.04, 0.32)
Relative Risk (Topical/None): 5%/55% = 0.10, 95 % CI (0.04, 0.26)
Relative Risk (Oral/None): 44%/55% = 0.81, 95% (0.58, 1.12)
(Similar adjusted relative risks in the regression analysis)

Secondary Outcomes
There was statistically significant decrease in the topical group in duration of initial episode, median number of days with otorrhea over 6 months and recurrence. There was no difference in general or disease-specific quality of life at two weeks between the treatment groups

Adverse Events
There were no infectious complications at two weeks in either group. 21% of the topical group had pain on administration. 23% of the oral group had gastrointestinal adverse effects

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The 95% confidence intervals for the risk difference and relative risks are presented above. Confidence intervals for a risk difference (A-B) that do not include 0 are statistically significant. Confidence intervals for a relative risk (A/B) that do not include 1 are statistically significant.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Maybe. This was a study of European patients. Table 1 includes the breakdown of organisms involved. It indicates a very low percentage of Strep pneumoniae when compared to the US. The authors state that they chose a low dose of the Amoxicillin component of Amoxicillin/Clavulanate due to lower resistance in their population.
Were all clinically important outcomes considered?	Yes. The author's primary outcome was treatment failure defined as otorrhea in one or both ears by otoscopy at the 2-week follow up. Secondary outcomes included other measures of efficacy such as duration of discharge. In addition, parents completed two quality of life questionnaires (general and disease specific). Adverse events were reported.
Are the likely treatment benefits worth the potential harm and costs?	Yes. Potential benefits of topical therapy include less systemic effects and a reduction of the impact of antibiotics on bacterial resistance. The study demonstrated no serious infectious complication of otitis media. 21% of patients in the topical group had pain on administration. 23% of the oral antibiotic group had gastrointestinal symptoms. The number needed to treat for the comparison of topical to oral treatment is 3. Three patients would need to be treated topically in order to prevent 1 additional treatment failure compared to oral antibiotics. The number needed to treat for the comparison of topical to observation is 2. Two patients would need to be treated topically in order to prevent 1 additional treatment failure compared to observation only.

CLINICAL BOTTOM LINE

BACKGROUND: Tympanostomy tubes are used to improve hearing in children with persistent otitis media with effusion and to decrease the recurrence of acute otitis media. Topical therapy (ear drops) is an option available in children with otorrhea and tympanostomy tubes that is not available to those with acute otitis media and an intact tympanic membrane.

CLINICAL QUESTION: In children with tympanostomy tubes and an acute onset of otorrhea, what is the effectiveness of topical antibiotics with a corticosteroid when compared to oral antibiotics or a strategy of observation without treatment in reducing treatment failures?

DESIGN/VALIDITY: This was a well-designed, open label, pragmatic clinical trial that included 230 patients in the primary analysis. There were no significant design flaws. A topical group without corticosteroids was not included in the design. The lack of blinding could have influenced the measurement of some of the outcomes. An oral placebo and topical placebo may have reduced the risk of this bias. A regression analysis was completed to account for potential differences in the treatment groups. Pragmatic trial assess effectiveness under real life conditions

PRIMARY RESULTS: There was a statistically and clinically significant reduction in treatment failure with topical antibiotics with corticosteroids when compared to both the oral antibiotic group (Risk Difference (Topical – Oral) = 5 – 44 = -39%, 95% (-51, -26%) and the observation only group. (Risk Difference (Topical – None) = 5 – 55 = -49%, 95% CI (-62, -37%). The authors considered a 20% difference in risk of treatment failure to be clinically significant. There was not a statistically significant difference between the oral antibiotic group and the observation only groups (Risk Difference (Oral – None) = 44 – 55 = -11% 95% CI (-27, 5%)). Of note, nearly half of the no treatment group was not considered a treatment failure. (resolved without treatment).

There was also a statistically significant reduction in the secondary outcomes for the topical group in the duration of initial episode, median number of days with otorrhea over 6 months and recurrence. The reduction in the clinical outcomes were not associated with statistically significant improvement in the patient oriented outcomes of the general or disease-specific quality of life. No infectious complications were seen in either group. The pain of administration of the topical therapy is likely offset by the gastrointestinal symptoms in the oral therapy group.

APPLICABILITY: Differences in the epidemiology and resistance in this European population may affect the applicability to our population. The number needed to treat to prevent an additional treatment failure is very low (3 for the topical/no therapy comparison and 2 for the topical/oral comparison).

AUTHOR'S CONCLUSION: "Antibiotic–glucocorticoid eardrops were more effective than oral antibiotics and initial observation in children with tympanostomy tubes who had uncomplicated acute otorrhea."

POTENTIAL IMPACT: The low rate of adverse events, the potential to reduce bacterial resistance and high rate of benefit as indicated by the very large risk differences and low numbers needed to treat make topical therapy with antibiotics and corticosteroids an attractive option for those with tympanostomy tubes and otorrhea. Cortisporin otic suspension (Neomycin, Polymixin B and Hydrocortisone) or Ciprodex otic suspension (Ciprofloxacin and Dexamethasone) could likely be substituted for the study medication in the US. The topical intervention was a composite of antibiotics and corticosteroids. It is unclear which of the components or if both combined is responsible for the benefit seen in this study.

SINUSITIS:
AMOXICILLIN/CLAVULANATE VS PLACEBO

In children diagnosed with acute bacterial sinusitis based of stringent clinical criteria without performance of confirmatory radiographs will treatment with Amoxicillin/Clavulanate when compared to Placebo result in an increase in the clinical cure rate?

Svetlana Sabel, M.D., Sabrina Gmuca, M.D., Michael Mojica, M.D.

August 2012

Wald ER, Nash D, Eickhoff J.

EFFECTIVENESS OF AMOXICILLIN/CLAVULANATE POTASSIUM IN THE TREATMENT OF ACUTE BACTERIAL SINUSITIS IN CHILDREN.

Pediatrics. 2009 Jul;124(1):9-15.
PubMed ID: 19564277

STUDY DEFINITIONS	
POPULATION	Inclusion: 1-10 years of age with 1 of 3 clinical presentations compatible with acute bacterial sinusitis (ABS) with persistent, acutely worsening or severe symptoms 1. Persistent: Nasal discharge or daytime cough for 10 days without improvement. 2. Worsening: Nasal discharge or daytime cough that was worsening on or after the sixth day, new-onset fever (≥ 100.5°F) or increase in nasal discharge or cough after transient improvement of symptoms 3. Severe: Temperature ≥102°F and purulent nasal discharge for ≥ 3 days. Exclusion: 1. Received antibiotics within 15 days 2. symptoms for 30 days 3. concurrent bacterial infection 4. allergic to penicillin 5. Complication of ABS requiring hospitalization, intravenous antibiotics, subspecialty evaluation 6. immunodeficiency or anatomic abnormality of the upper respiratory tract. Setting: 2 private pediatric practices (1 rural, 1 urban) and a hospital-based clinic. 1/2004-6/2006
INTERVENTION	Amoxicillin (90 mg/kg)/Clavulanate (6.4m g/kg) divided BID (max 4 grams/day)
CONTROL	Placebo divided BID
OUTCOME	Primary Outcome: Proportion cured on day 14 Symptom score (see appendix) by phone on day 0, 1, 2, 3, 5, 7,10, 20, 30 Cured: Score was 2 Improved: Score decreased by at least 50%. Treatment failure: Score increased by 4, scores were not reduced at 48 hours (entry score minus at least 2 points), score not improved by 72 hours (score 50% of the score at entry), score was 5 at 14 days. Secondary Outcomes: Proportion with treatment failures Proportion with antibiotic effects: rash, diarrhea, vomiting, abdominal pain.
DESIGN	Interventional: Randomized clinical trial

ARE THE RESULTS VALID?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. “Patients were randomly assigned to receive either Amoxicillin/potassium Clavulanate or Placebo on a 1:1 basis in blocks of 4. The allocation sequence was generated by the principal investigator”
Was randomization concealed?	Unclear. The authors did not describe the method of allocation concealment.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. (Table 2) The patients were similar in age, gender, race, presentation, and severity.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded	Yes. “participants, research nurses, and physicians were blinded to group assignments” There was not a description of the characteristics of the placebo (taste, appearance) compared to Augmentin
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	No. In the antibiotic group 6/28 (21%) patients were lost follow up. None were lost in the placebo group. Consumption of at least 80% of the medication was considered to be compliant
Were patients analyzed in the groups to which they were randomized?	Yes. The study included both an Intention to treat and per protocol analysis (see Figure 1). It would have been helpful to see a sub-analysis based on the three presentations of ABS defined in the study (severe, worsening and persistent) and by patient age
Was the trial stopped early	No, the trial was not stopped but patients who failed, were removed from the study and given an alternative antibiotic: (Cefpodoxime) in order to assure that the placebo group received antibiotics if needed.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

PRIMARY OUTCOME: CLINICAL CURE (INTENTION TO TREAT)

	CLINICAL CURE		
	YES	NO	
AUGMENTIN	14	14	28
PLACEBO	4	24	28
	18	38	56

Risk (Antibiotics) = 14/28 = 50%.
Risk (Placebo) = 4/28 = 14%
Risk Difference = (Placebo–Antibiotics) = (14%-50%) = - 36%, 95% CI (-55.1, -11.3%)
Relative Risk (Antibiotics/Placebo) = 50/14 = 3.6, 95% CI (1.3, 9.3)

Adverse Events:
More common in antibiotics group (44% vs 14%).
Self-limited diarrhea. Not statistically significant

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence intervals were not provided in the article but were calculated online and are included below. While both confidence intervals indicate a statistically significant result they are very wide as the result of the small sample size
Risk Difference = 36%, 95% CI (11, 55%), Statistically significant, doesn't include 0
Relative Risk = 3.6, 95% CI (1.3, 9.3), Statistically significant doesn't include 1

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Somewhat. Patients are predominately white. Study was performed at 2 private pediatric practices (1 rural, 1 urban) and a hospital-based clinic in the Pittsburgh area
Were all clinically important outcomes considered?	No. The small sample size precluded an analysis of the effect of antibiotics on rare but serious complications of sinusitis. It would have been helpful to see a sub-analysis based on age, setting, and day of illness on presentation.
Are the likely treatment benefits worth the potential harm and costs?	NNT= 1/ARD = 1/(0.36) = 2.7 95% CI (2, 9). Need to treat 2-3 people with antibiotics to have 1 additional clinical cure compared to no antibiotics. Rare but serious complications of sinusitis could not be assessed.

CLINICAL BOTTOM LINE

BACKGROUND: The efficacy of treatment of acute bacterial sinusitis with antibiotics has not been proven. This in part may be due to the fact the there is no gold standard for diagnosis and the inclusion of patients without bacterial infection in treatment studies may decrease the impact of therapy. This placebo controlled, randomized clinical trial utilized strict clinical criteria to compare the efficacy of high dose Amoxicillin/Clavulanate to placebo for acute bacterial sinusitis

CLINICAL QUESTION: In children diagnosed with acute bacterial sinusitis based of stringent clinical criteria without performance of confirmatory radiographs will treatment with Amoxicillin/Clavulanate when compared to Placebo result in an increase in the clinical cure rate?

DESIGN/VALIDITY: This was double blind, placebo controlled randomized trial that occurred in an outpatient (non-ED) setting. The study was well-designed and primarily suffered from a small sample size (n = 56, 28 per group) with approximately 20% of patients being lost from the antibiotic group.

PRIMARY RESULTS: The study demonstrated a clinically and statistically significant benefit of Amoxicillin/Clavulanate when compared to placebo. The antibiotic group had a 36% higher clinical cure rate. Only 2-3 patients would need to be treated to result in 1 additional cure when compared to placebo. Of concern is the absolute rate of cure in the antibiotic group of only 50% (increased to 70% if both “cured” and “improved” outcomes included). Adverse events were more common in the antibiotic group (44% vs 14%) though this difference was not statistically significant. The most commonly consisted of self-limited diarrhea.

APPLICABILITY: The small sample size, non-ED setting and low absolute cure rate of antibiotics may limit the generalizability of this studies results.

AUTHOR’S CONCLUSION: “Acute bacterial sinusitis is a common complication of viral upper respiratory infections. Amoxicillin/potassium clavulanate results in significantly more cures and fewer failures than placebo, according to parental report of time to resolution of clinical symptoms.”

POTENTIAL IMPACT: There was a statistically and clinically significant improvement in the clinical cure of sinusitis in the antibiotic group. Attention to the American Academy of Pediatrics and the Infectious disease society of American may assist in determining who has acute bacterial sinusitis and therefore who is most likely to benefit from antibiotics.

APPENDIX: SYMPTOM SCORE

CLINICAL SEVERITY SCORE	
Abnormal nasal of postnasal discharge: Minimal	1
Abnormal nasal of postnasal discharge: Severe	2
Nasal congestion	1
Cough	2
Malodorous	1
Facial tenderness	3
Erythematous nasal mucosa	1
Fever < 38.5C*	1
Fever ≥ 38.5 C*	2
Head (retro-orbital)/Irritability: Severe	3
Head (retro-orbital)/Irritability: Mild	1
Score < 8 = mild, ≥ 8 = severe *Within 24 hours of presentation, observed, according to history and documented with thermometer	

UPPER RESPIRATORY INFECTION: ACETAMINOPHEN PLUS IBUPROFEN

In children 6 months–6 years of age with a temperature between 37.8 C (100 F) and 41.0 C (105.8 F) and who appear unwell, which antipyretic regimen: Acetaminophen and Placebo, Ibuprofen and Placebo or Acetaminophen and Ibuprofen results in a greater time without fever over a 4-hour period?

Carrie Danziger, M.D., Dennis Heon, M.D.
December 2008

Hollinghurst S, Redmond N, Costelloe C, Montgomery A, Fletcher M, Peters TJ, Hay AD.

PARACETAMOL PLUS IBUPROFEN FOR THE TREATMENT OF FEVER IN CHILDREN (PITCH): RANDOMIZED CONTROL TRIAL.

BMJ. 2008 Sep 9;337: a1490.
PubMed ID: 18782838

STUDY DEFINITIONS	
POPULATION	Inclusion: 6 months-6 years, “unwell”, temperature ≥ 37.8°C and ≤ 41.0°C, illnesses that could be managed at home. Unwell defined as: discomfort, reduced activity, abnormal appetite, or abnormal sleep. Exclusion: Required hospital admission, clinically dehydrated, recently participated in another trial; had previously participated in PITCH, known intolerance, allergy, or contraindication to a trial drug; chronic neurological, cardiac, pulmonary (except asthma), liver, or renal disease, parents who could not read or write in English. Setting: Recruited from private practice, urgent care, ED and through direct advertisement to parents. 1/2005-5/2007
INTERVENTION	Acetaminophen: 15 mg/kg Q4-6 Hours (maximum 4 doses/24 hours) given on a standing basis for the first 24 hours then PRN from 24-48 hours AND Ibuprofen: 10 mg/kg Q6-8 Hours (maximum 3 doses/24 hours) given on a standing basis for the first 24 hours then PRN from 24-48 hours (A/I group)
CONTROL	1. Acetaminophen (see dosing above) and Placebo (A/P group) 2. Ibuprofen (see dosing above) and Placebo (I/P group)
OUTCOME	Primary Outcomes: 1. Number of minutes without fever (<37.2°C) in the first 4 hours 2. Proportion reported as being normal on the discomfort scale at 48 hours. Secondary outcomes: 1. Time to temperature first falling below 37.2°C (fever clearance) in 1st 24 hours 2. Time spent without fever over 24 hours 3. Proportion of children without fever associated symptoms: discomfort, reduced activity, reduced appetite, disturbed sleep. 4. Adverse effects. Note: Temperature recorded Q30 seconds with an axillary probe
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized to one of 3 study arms by a remote automated randomization service. Allocation done by “minimization” to assure similar groups for age, severity of fever, duration of fever, discomfort scale, antibiotic use.
Was randomization concealed?	Yes. Group allocation was concealed.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Table 1, Groups were very similar except for gender, methods of recruitment, and activity.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The authors state that the parents were blinded yet parents were aware because of the differences in dosing, in the Acetaminophen/Placebo, and Ibuprofen/Placebo groups. In addition, 27% of parents correctly guessed allocation (this percent increases to 49% when parents who said “I don’t know” were removed. Clinicians were not blinded. Research nurses were blinded to allocation.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Attrition was minimal. Based on Figure 2, nearly 100% of patients were assessed for the primary outcomes. Some data points such as mean temperature at 48 hours (for 8 subjects) and follow up information on day 5 (for 18 subjects) was unknown or incomplete.
Were patients analyzed in the groups to which they were randomized?	Yes. An intention to treat analysis was performed.
Was the trial stopped early?	Yes. The Trial was stopped early due to recruitment difficulties. The original sample size determination required 747 children.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 156 (52 in each of the 3 study groups)

Primary Outcome

TIME WITHOUT FEVER IN FIRST 4 HOURS	
STUDY GROUP	MINUTES (SD)
Acetaminophen/Ibuprofen (A/I)	171.1 (40.8)
Acetaminophen/Placebo (A/P)	116.2 (65.0)
Ibuprofen/Placebo (I/P)	156.0 (57.6)

Mean Difference:
A/I (171.1) – A/P (116.2) = 54.8 (33.1, 77.5) minutes
A/I (171.1) – I/P (156) = 15.1 (-4.4, 34.6) minutes
I/P (156) – A/P (116.2) = 40 (18, 61) minutes
The authors considered a 30-minute difference to be clinically significant in their sample size determination
Mean Difference: Time without fever in 24 hours
A/I – A/P = 4.4 (2.4, 6.3) hours

NORMAL ON DISTRESS SCALE AT 24 HOURS	
STUDY GROUP	PROPORTION
Acetaminophen/Ibuprofen (A/I)	69%
Acetaminophen/Placebo (A/P)	65%
Ibuprofen/Placebo (I/P)	71%

SECONDARY OUTCOMES (SEE TABLE 2)			
	A/P	I/P	A/I
Time to temp < 37.2C (min)	71.0	42.2	45.5
Time without fever in 24 hours (min)	940	1055	1217
% without fever symptoms 24 hours	22	36	29

A/I – I/P = 2.5 (0.6, 4.4) hours

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The 95% confidence for the mean and risk differences are presented above.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Somewhat. Patients were 6 months - 6 years with fever in primary care and household settings. Fever defined differently than we do in the ED, as axillary T ≥ 37.8. Fever clearance was defined as when the temperature fell below 37.2.
Were all patient important outcomes considered?	Yes. It would have been helpful to record discomfort at 4 hours to correlate with the primary outcome of difference in time without fever at 4 hours?
Are the likely treatment benefits worth the potential harm and costs?	Although minimal side effects in all groups, maximum doses were exceeded at 24 hours in 13% of patients. This raises concern that if parents are told to give both medications, they may exceed maximum dosing for both drugs Only 73% received the recommended dose in 24 hours. There was no correlation between discomfort and time without fever. Unclear if time without fever is clinically significant in this “unwell” cohort. Adverse effects were mild and equally distributed between study groups. 5 admissions were deemed to attributable to the study medications.

CLINICAL BOTTOM LINE

BACKGROUND: The management of fever in children has become controversial with the initiation of Ibuprofen as alternative to acetaminophen. Prior studies have indicated that ibuprofen may provide a statistically significant decrease in fever when compared to Acetaminophen though the clinical significance of this decrease is unclear. Studies have also demonstrated the degree of “fever phobia” that many caregivers have. Many clinicians and caregivers recommend that both medications be used together though little evidence supports this practice.

CLINICAL QUESTION: In children 6 months–6 years of age with a temperature between 37.8 C (100 F) and 41.0 C (105.8 F) and who appear unwell, which antipyretic regimen: Acetaminophen and Placebo, Ibuprofen and Placebo or Acetaminophen and Ibuprofen results in a greater time without fever over a 4 hour period?

DESIGN/VALIDITY: This was a well-designed clinical trial analyzing the potential benefits of both Ibuprofen and Acetaminophen in febrile children with a presumed infectious etiology of fever. They utilized an every 30-second axillary temperature monitor to record fever related variables. The trial was stopped early due to difficulties with recruitment.

PRIMARY RESULTS: There was a statistically significant decrease in the primary outcome of time without fever in the 1st 4 hours when comparing the Acetaminophen and Ibuprofen group (171.1 minutes) to the Acetaminophen and Placebo group (116.2 minutes). Difference of 54.8 minutes, 95% (33.1, 77.5 minutes). There was also a statistically significant decrease in the primary outcome of time without fever in 1st 4 hours when comparing the Ibuprofen and Placebo group (156.0 minutes) to the Acetaminophen and Placebo group (116.2 minutes). Difference of 40 minutes, 95% CI (18, 61 minutes). The authors considered a 30-minute difference to be clinically significant. Whether a 40 or 55-minute difference is also clinically significant is unclear.

There was no statistically significant difference in the primary outcome of time without fever in 1st 4 hours when comparing the Acetaminophen and Ibuprofen group (171.1 minutes) to the Ibuprofen and Placebo group (156.0 minutes). Difference of 15.1 minutes, 95% CI (-4.4, 34.6 minutes). This difference was neither statistically or clinically significant.

The time without fever in 24 hours was lowest in the Acetaminophen and Ibuprofen group when compared to the Acetaminophen and Placebo group (Difference: 4.4 (2.4, 6.3) hours) and when compared to the Ibuprofen and Placebo group (Difference: 2.5 (0.6, 4.4) hours). However, there was no statistically significant difference in the proportion of children normal on distress scale at 24 hours.

APPLICABILITY: Issues with temperature criteria, the entry criteria of “unwell”, referral setting and medication compliance may make this somewhat difficult to apply to our population.

AUTHOR’S CONCLUSION: “Doctors, nurses, pharmacists, and parents wanting to use medicines to treat young, unwell children with fever should be advised to use ibuprofen first and to consider the relative benefits and risks of using paracetamol plus ibuprofen over a 24-hour period. There is no evidence from the accompanying cost effectiveness evaluation to contradict these findings.”

POTENTIAL IMPACT: Ibuprofen and the combination of Ibuprofen with Acetaminophen was superior to Acetaminophen in reducing the time without fever in the first 4 hours. The combination of Ibuprofen with Acetaminophen was superior to either antipyretic alone in reducing the time without fever in 24 hours. However, the proportion of children considered normal on a distress scale at 24 hours was similar in all treatment groups. It appears that there is a clear benefit of Ibuprofen over Acetaminophen. The combination of both antipyretics may have some benefits but the complexity of given both with different frequencies may not offset the potential benefits.

UPPER RESPIRATORY INFECTION: COUGH/COLD MEDICATIONS

In patients 2-18 years of age with an acute cough due to an upper respiratory tract infection does the administration of Diphenhydramine or Dextromethorphan when compared to Placebo improve parental assessment of nocturnal cough?

Michael Mojica, M.D.
July 2017

Paul IM, Yoder KE, Crowell KR, Shaffer ML, McMillan HS, Carlson LC, Dilworth DA, Berlin CM Jr.

EFFECT OF DEXTROMETHORPHAN, DIPHENHYDRAMINE, AND PLACEBO ON NOCTURNAL COUGH AND SLEEP QUALITY FOR COUGHING CHILDREN AND THEIR PARENTS

Pediatrics. 2004 Jul;114(1): e85-90.
PubMed ID: 15231978

STUDY DEFINITIONS	
POPULATION	Inclusion: 2-18 years of age, cough attributed to an upper respiratory tract infection (URI). URI characterized by the presence of rhinorrhea and cough for ≤ 7 days. Other included symptoms: congestion, fever, sore throat, myalgias, and headache. Children who had comorbid diagnoses of otitis media or streptococcal pharyngitis and were prescribed antibiotics and were not excluded Symptom severity criteria: Parents who answered at least “somewhat” (3 points) for a minimum of 2 of 3 questions related to nocturnal cough on the night prior to presentation (See Appendix) Exclusion: 1. Signs or symptoms of a treatable disease: Asthma, pneumonia, sinusitis laryngotracheobronchitis,allergic rhinitis. 2. History: Asthma, chronic lung disease, allergic rhinitis. 3. Taken an antihistamine or dextromethorphan the evening before enrollment or within 8 hours of bedtime on the day of enrollment. 4. Concurrent use of drugs that are known to inhibit cytochrome P450 2D6, such as serotonin-selective reuptake inhibitors. Setting: 2 university affiliated pediatric practices, 6/2002-5/2003
INTERVENTION	Diphenhydramine: 1.25 mg/kg/dose (maximum 50 mg/dose) OR Dextromethorphan: 2-5 years: 7.5 mg/dose, 6-11 years: 15 mg/dose, 12-18 years: 30 mg/dose.
CONTROL	Placebo
CO-INTERVENTIONS	Study intervention or controls administered 30 minutes before sleep Analgesic medications such as Acetaminophen or Ibuprofen were permitted
OUTCOME	Change in Symptom Score: Baseline – After study intervention or control Parental survey of nighttime cough: 7 point Likert scale. Frequency, ability to sleep (patient and parent), severity, how bothersome on a (See Appendix)
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Randomization was stratified by age as 2-5 years, 6-11 year, 12-18 years. The randomization method was not described.
Was randomization concealed?	Yes. The medications were distributed by the pharmacy in a brown paper bag to mask the investigators to the volume of medication. A description of the placebo was not provided.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. See Table 1. Patients were similar at baseline with regard to age, race, gender, duration of illness, cough parameters and a combined symptom score.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Unclear. The study is described as “double masked”. It states that the medications were distributed by the pharmacy in a brown paper bag to mask the investigators to the volume of medication. It does not state how the parents were masked.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Unclear. The study states that “one hundred children with URIs were enrolled and completed the single-night study.” It does not state if there were patients enrolled who did not complete the study.
Were patients analyzed in the groups to which they were randomized?	Unclear. See response above. If no patients were enrolled that did not complete the study then the analysis is an intention to treat analysis. Compliance with study medications (e.g. due to vomiting) was not assessed.
Was the trial stopped early?	No. The trial was not stopped early.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

	NIGHT 1	NIGHT 2	DIFFERENCE*
	No Medication	Medication or Placebo	
Frequency	3.94 ± 1.02	1.88 ± 1.54	2.06
Child sleep	3.88 ± 1.21	1.65 ± 1.58	2.23
Parent sleep	4.10 ± 1.17	1.53 ± 1.54	2.57
Bothersome	3.91 ± 1.30	1.80 ± 1.60	2.11
Severity	4.00 ± 0.94	2.07 ± 1.66	1.93
COMBINED	19.83±4.09	8.93 ± 7.11	10.9
*All differences p < 0.001			

A 1 point difference in symptom score was considered clinically significant by the authors in their sample size determination. The average decline in symptom score was 2.2 (10.9/5).
1 patient in each group was subsequently treated for a bacterial infection.

IMPROVEMENT BY STUDY GROUP			
	DIPHENHYDRAMINE	DEXTROMETHORPHAN	PLACEBO
Frequency	-1.97		-2.24
Child sleep	-2.64	-1.88	-2.18
Parent sleep	-2.67	-2.45	-2.59
Bothersome	NA	NA	NA
Severity	-2.06	-1.85	-1.88
COMBINED	-11.79	-10.06	-10.85
No significant difference between groups. Figure 2			

ADVERSE EVENTS			
	DPH	DM	PL
Disorientation	0%	0%	2.9%
Dizziness	0%	3%	0%
Drowsiness	10%	0%	0%
Headache	3%	0%	0%
Hyperactivity	10%	20%	15%
Insomnia	0%	10%	0%
Nervousness	3%	3%	0%
Abd pain/nausea	3%	6%	8.9%
No significant difference between groups. Table 3			

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?
Confidence intervals for the difference between the treatment groups were not provided.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Likely yes. The study setting was two pediatric practices and upper respiratory tract infection should be similar in the ED setting. However, we may care for a population with a higher likelihood of co-morbid conditions.
Were all patient important outcomes considered?	Yes. However, days lost from work or school or impairment in the ability to eat and drank are patient oriented outcomes that were not assessed.
Are the likely treatment benefits worth the potential harm and costs?	There was no demonstrated benefit comparing either of the study medications to placebo. However, there were many adverse events documented. There were no statistically significant differences in adverse events likely due to insufficient power.

CLINICAL BOTTOM LINE

BACKGROUND: Cough and cold symptoms generate a great deal of parental anxiety. Symptoms can lead to a generally ill appearing child with difficulty eating and sleeping. Cough and cold medicines have been used for pediatric upper respiratory tract symptoms without sound evidence of their efficacy. These medications can have significant side effects. In addition, lethargy or irritability because of medications can be confused as serious illness. The combination of a lack of proven benefit and potential for toxicity has lead organizations such as the American Academy of Pediatrics to not recommend cough and cold medications.

CLINICAL QUESTION: In patients 2-18 years of age with an acute cough due to an upper respiratory tract infection does the administration of Diphenhydramine or Dextromethorphan when compared to Placebo improve parental assessment of nocturnal cough?

DESIGN/VALIDITY: This was a randomized clinical trial assessing the effect of Dextromethorphan or Diphenhydramine compared to Placebo on parentally assessed night time cough. It included 100 patients (33 Dextromethorphan, 33 Diphenhydramine, 34 Placebo) in the primary analysis.

There are several validity concerns.
1. The randomization method is not presented
2. The method used to blind the parents were not presented.
3. It is unclear if the cough survey utilized has been previously validated.
4. A description of the placebo was not provided.
5. Compliance with study medications (e.g. due to vomiting) was not assessed.
It is unclear if these are issues with the study methodology or in reporting the methodology.

PRIMARY RESULTS: Patients had an average of a 2.2-point decrease in each of the 5 cough symptoms scores. However, there was no difference in improvement when comparing the three study groups: Diphenhydramine, Dextromethorphan and Placebo. Since there was no difference between the medication and placebo group the improvement may due to natural course of disease improvement. Patients presented on average 4.2 days into their illness and uncomplicated upper respiratory tract infection typically last between 4 and 6 days. The lack of difference in efficacy presumes there is not a significant placebo effect.

There were many adverse events documented. However, there were no statistically significant differences in adverse events between the three study groups. This may be due to insufficient power to assess difference in rare outcomes.

APPLICABILITY: The study setting was two academically affiliate pediatric practices and upper respiratory tract infection should be similar in the emergency department setting. However, we may care for a population with a higher likelihood of co-morbid conditions. Days lost from work or school or impairment in the ability to eat and drank are patient oriented outcomes that were not assessed.

AUTHOR'S CONCLUSION: "The desire to ease symptoms is strong for both parents and clinicians. This investigation supports the concept that URIs are self-limited illnesses that improve with time. It also questions whether common OTC medications have a place in the treatment of these illnesses for children. Each clinician should consider these findings, the potential for adverse effects, and the individual and cumulative costs of the drugs before recommending them to families."

POTENTIAL IMPACT: No large controlled trials studies have convincingly documented the efficacy of cough and cold medication marketed to children. However, multiple adverse events, primarily related to dosing errors, have been reported. This randomized trial, despite some methodologic concerns demonstrates the lack of efficacy and potential for adverse events. Two children (2%) were subsequently diagnosed and treated for bacterial infections. While most viral upper respiratory tract infections are self-limited it is important to consider bacterial superinfection if symptoms last longer than anticipated or new symptoms develop.

In 2007, the FDA's advisory concluded that evidence from pediatric studies was insufficient to prove the efficacy of cold and cough medications in children. In 2008, the FDA recommended that over-the-counter cough and cold medications not be used in children under 2 years of age because of the risk of serious, life-threatening adverse events and should be used with caution, if at all, in those less than 4 years of age. (Sharfstein, NEJM 2007, PubMed ID: 18057333). These recommendations are supported by the American Academy of Pediatrics.

APPENDIX: NOCTURNAL COUGH SURVEY

SURVEY QUESTIONS TO ASSESS NOCTURNAL COUGH LAST NIGHT						
1. How frequent was your child's cough last night?						
2. How much did last night's cough affect your child's ability to sleep?						
3. How much did last night's cough affect your ability to sleep?						
4. How severe was your child's cough last night?						
5. How bothersome was last night's cough to your child?						
Extremely*	Very Much	A lot	Somewhat	A little	Occasional	Not at all
6	5	4	3	2	1	0
*The frequency question substitutes the phrase CONSTANT for EXTREMELY						

HEMATOLOGY & ONCOLOGY

1. Sickle Cell: Bacteremia: J Pediatr Hematol Oncol. 2002

SICKLE CELL DISEASE:
FEVER AND BACTEREMIA

In febrile pediatric patients with sickle cell disease, do clinical and laboratory parameters accurately identify those with and without bacteremia?

Michael Mojica M.D.
May 2017

West DC, Andrada E, Azari R, Rangaswami AA, Kuppermann N.

PREDICTORS OF BACTEREMIA IN FEBRILE CHILDREN WITH SICKLE CELL DISEASE

J Pediatr Hematol Oncol. 2002 May;24(4):279-83.
PubMed ID: 11972096

STUDY DEFINITIONS

POPULATION	Inclusion: < 18 years, sickle cell disease (SS, SC or sickle-thalassemia), presenting to an ambulatory site (clinic, ED, urgent care). Temperature > 38C (100.4 F), blood culture sent Exclusion: None presented Setting: Single Children's Hospital, 1/1989-1/1999
TEST	Age, temperature, sickle cell disease type, total white blood cell (WBC) count, absolute neutrophil count (ANC) and absolute band count (ABC).
REFERENCE STANDARD	Bacteremia: (+) Blood culture. Contaminant: Organism cultured was coagulase-negative *Staphylococcus* or another common skin flora, such as alpha-hemolytic *Streptococcus*, in a patient without a central venous catheter)
OUTCOME	Adjusted odds ratio of predictors
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?

Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Unclear. When a patient with sickle cell disease presents with a fever it is unknown if they are bacteremic. However, clinical parameters such a blood pressure and physical exam findings can increase the pre-test probability of bacteremia. These factors could not be assessed due to the retrospective design of the study.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. Bacteremia was clearly defined as was criteria for a contaminated culture. The test results are objective and included: age, fever, sickle cell type and white cell count variants (WBC, ANC, ABC).
Were those interpreting the test and reference standard blind to the other results?	This was a retrospective cohort by chart review. It is possible that those reviewing the chart were aware of the presence or absence of bacteremia prior to determining the clinical and laboratory data. However, both the tests included and the outcome are objective. It is highly unlikely that lack of blinding to the test results would influence the blood culture result.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	Yes. Only patients with a blood culture sent were included. One febrile episode was excluded because a blood culture was not available.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

57 patients had 175 febrile events.
Bacteremia: 8/175 (4.6%)
6 of 8 described as “not ill-appearing”

3 regression analyses were conducted controlling for age and temperature each with one of the three CBC parameters (WBC, ANC and ABC) to avoid multicollinearity).

Age and temperature were not independent predictors of bacteremia in any of the models.

Each component of the CBC was a significant, independent predictor of bacteremia. The adjusted odds ratios are presented in the table below.

TEST	ADJUSTED ODDS RATIO (95% CI)	
WBC	1.47 (1.01, 2.16)	Per each ↑ by 5,000/mm^3
ANC	1.71 (1.13, 2.59)	Per each ↑ by 5,000/mm^3
ABC	1.4 (1.09, 1.80)	Per each ↑ by 1,000/mm^3
GREEN = STATISTICALLY SIGNIFICANT, RED = NOT STATISTICALLY SIGNIFICANT		

Test characteristics were not provided for either the overall accuracy of the CBC parameters (e.g. area under the receiver operating characteristic curve) or for specific cutoff points for each test.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Yes. All the statistically significant independent predictors of bacteremia are objective laboratory findings.
Are the study results applicable to the patients in my practice?	Yes. The results should be applicable to our pediatric sickle cell patients. However, the pre-test probability of bacteremia has likely decreased due to the use of the pneumococcal protein conjugate vaccines (Prevnar 7, Prevnar 13).
Will the test results change my management strategy?	No. Test cutoffs were not provided for the predictors.
Will patients be better off as a result of the test?	Theoretically, patients with low risk parameters may be able to be managed as outpatients with antibiotics pending culture results if they can reliably return for care if clinical deterioration occurs.

CLINICAL BOTTOM LINE

BACKGROUND: Patients with sickle cell disease and fever have an increased risk of bacteremia particularly with encapsulated organisms such as Streptococcal pneumoniae. While prophylactic antibiotics and vaccines can decrease the risk of bacteremia they do not completely exclude the possibility. At the time of this study, the common practice was to admit most febrile patients with sickle cell disease for intravenous antibiotics until cultures were negative. The ability to identify a subset of well appearing patients at low risk for bacteremia would possibly allow for outpatient management of these patients with antibiotics pending culture results.

CLINICAL QUESTION: In febrile pediatric patients with sickle cell disease, do clinical and laboratory parameters accurately identify those with and without bacteremia?

DESIGN/RISK OF BIAS: The was a retrospective cohort study of a sickle cell clinic population at a single pediatric hospital. The cohort included 128 patients of which 57 had 175 febrile events. The Bacteremia rate for febrile events was 4.6% (8/175). The primary validity concern was that no clinical parameters other than age, fever and type of sickle cell disease were including in the analysis. Therefore, it is unclear whether the tests are being applied to patients with a high degree of diagnostic uncertainty. For example, the utility of a white blood cell count would be reduced in a patient who was hypotensive with purpura and altered mental status. In addition, patients were placed on twice daily penicillin and compliance could not be assessed retrospectively.

PRIMARY RESULTS: Three CBC parameters (WBC, ABC and ANC) were statistically significant independent predictors of bacteremia in the regression models. However, test characteristics at specific cutoffs were not presented due to the low number of febrile episodes with bacteremia. Age and temperature were not independent predictors of bacteremia in any of the models.

APPLICABILITY: Of the 167 febrile episodes 140 (84%) were in patients with sickle cell SS. All cases of bacteremia occurred in patients with sickle cell SS. In addition, 4 of the 8 cases of bacteremia (Steptoccocal pneumoniae (3) and Haemophilus influenzae (1)) would likely not occur today due to vaccination. It is difficult to generalize the predictive abilities of the CBC parameters to patients with other types of sickle cell disease (SC. S-Thal).

AUTHOR'S CONCLUSION: "In febrile children with sickle cell disease, WBC, ANC, and ABC are all independently associated with bacteremia when adjusting for height of fever and age. Hematologic variables may be useful in developing prediction algorithms to identify febrile patients with sickle cell disease at higher risk of bacteremia. These data emphasize the need for a national trial to develop a predictive model with defined thresholds."

POTENTIAL IMPACT: The study's results represent a very early step in identifying those patients with sickle cell disease and fever who are at low risk for bacteremia. The authors statement emphasizes that "a larger prospective study would allow one to determine which hematologic variable is the most important and the accuracy of different threshold cutoff thresholds in predicting bacteremia."

INFECTIONS

1. Febrile Children: Procalcitonin: Acad Emerg Med. 2014
2. Febrile Neonate: Boston Criteria: J Pediatr. 1992
3. Febrile Neonate: CBC Invasive Infection: JAMA Ped 2017
4. Febrile Neonate: PECARN Rule: JAMA Ped 2019
5. Febrile Neonate: Philadelphia Criteria: NEJM 1993
6. Febrile Neonate: Private Practice (PROS): JAMA 2004
7. Febrile Neonate: Procalcitonin: JAMA Pediatr. 2016
8. Febrile Neonate: RSV Serious Infection: Pediatrics 2004
9. Febrile Neonate: Rochester Criteria: J Pediatr. 1985
10. Febrile Neonate: Step-by-Step Rule Validate: Peds. 2016
11. Febrile Neonate: Urinalysis Accuracy: Pediatrics 2018
12. Influenza: Oseltamivir: BMJ 2014

FEBRILE CHILDREN: PROCALCITONIN

In well appearing, febrile infants and children (< 36 months) what are the test characteristics of Procalcitonin when compared to total WBC, absolute neutrophil count (ANC) and absolute band count (ABC) in identifying occult, serious bacterial infections (SBI)?

Nicole Gerber M.D., Jeffrey Fine, M.D.
April 5, 2016

Mahajan P, Grzybowski M, Chen X, Kannikeswaran N, Stanley R, Singal B, Hoyle J Jr, Borgialli D, Duffy E, Kuppermann N.

PROCALCITONIN AS A MARKER OF SERIOUS BACTERIAL INFECTIONS IN FEBRILE CHILDREN YOUNGER THAN 3 YEARS OLD.

Acad Emerg Med. 2014 Feb;21(2):171-9.
PubMed ID: 24673673

STUDY DEFINITIONS	
POPULATION	Inclusion: Convenience sample of well appearing, febrile children without an obvious source of fever < 36 months old. Documented fever (defined as (1) rectal temp in the ED or at home ≥ 38°C if ≤3 months of age or (2) ≥ 39°C if > 3 months of age), otherwise being evaluated for SBI with a blood culture. Exclusion: Antibiotic use in the previous 48 hours, obvious source of fever, known immunologic or systemic disease, history of prematurity (≤ 36 weeks) if < 3 months, any immunization in the previous 2 days, parent/guardian did not consent. Did not exclude patients with acute otitis media Setting: Multicenter, U.S. Children's Hospital EDs (PECARN). 5/2004-12/2005
DIAGNOSTIC TESTS	Procalcitonin, WBC count, Absolute neutrophil count, Absolute band count Standard cutoffs for dichotomous testing. Optimal cutoffs determined by ROC curve
REFERENCE STANDARD	Serious Bacterial Infection defined as: Bacteremia (+ blood culture) Bacterial meningitis (+ CSF culture) Lobar pneumonia (presence of focal infiltrate on chest radiograph), UTI (growth of a single known pathogen defined as: 1. ≥ 1,000 CFU/mL from a suprapubic aspiration specimen or 2. ≥ 50,000 CFU/mL from a bladder catheter specimen alone or 3. ≥ 10,000 CFU/mL from a bladder catheter specimen associated with a urine dipstick (a) positive for leukocyte esterase or nitrite or (b) >5 WBCs per high power field.).
OUTCOME	Test characteristics (dichotomous) and area under the receiver operating characteristic curves (continuous) for Procalcitonin, WBC, ANC and ABC
DESIGN	Observational Prospective cohort

ARE THE RESULTS VALID?	
Did participating patients present a diagnostic dilemma?	Yes. The patients were febrile children without an obvious source of fever. The source of the patient's fever could not be determined clinically.
Did investigators compare the test to an appropriate, independent reference standard?	The Procalcitonin values were compared to the gold standard of diagnosis of SBI: bacteremia, bacterial meningitis, lobar pneumonia or UTI (see definitions above)
Were those interpreting the test and reference standard blind to the other results?	The technicians performing the PCT were likely blinded as this was an outside lab. The investigators were not blinded to the Procalcitonin results, but the physicians who were evaluating the patients were blinded, as the Procalcitonin results were not available at the time of the ED evaluation. Additionally, as the Procalcitonin results were being compared to a gold standard of blood culture results (along with XRAY results, CSF culture results and urine culture results) knowledge of the test results would not impact the interpretation of the outcome.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	Yes. The Procalcitonin results were not available at the time of the initial patient evaluation, so all of the patients were evaluated and treated by the ED physician regardless of the PCT results. Not every child however, had every study. This is appropriate for the clinical workup of the patient's but it should be considered that while all of the children had a blood culture sent and 97% had a urine culture sent, 58% percent had CXR and 14% had CSF culture. Only 8% had all of the studies performed.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

SBI Rate = 13.3% (30/226)
UTI (8.2%), Pneumonia (6.0%), Bacteremia (1.7%), Meningitis (0.8%)

Grey cells in the tables indicate the higher test characteristic

TEST CHARACTERISTIC: DICHOTOMOUS TESTS (TABLE 2)

	WBC > 15,000	ANC > 10,000	ABC > 1,500	PCT > 0.5 ng/ml
SN	56.7% (38-74)	46.7% (29-65)	20% (8-39)	53.3% (35-71)
SP	76.3%(70-82)	88.1% (83-92)	93.3%(89-96)	90.1%(85-94)
PV(+)	27% (17-40)	38% (23-55)	32% (14-56)	46% (29-63)
PV(-)	92% (86-95)	91% (86-95)	88% (83-92)	86% (81-91)
LR(+)	2.4 (1.6-3.6)	3.94 (2.3-6.8)	2.99 (1.2-7.3)	5.39 (3.1-9.3)
LR (-)	0.6 (0.4-0.9)	0.61(0.4-0.9)	0.9 (0.7-1.0)	0.52 (0.4-0.8)

TEST CHARACTERISTIC: CONTINUOUS TESTS (TABLE 3)

	WBC > 19,000	ANC > 13,000	ABC > 1,800	PCT > 0.6 ng/ml
AUC	0.76 (0.66-0.86)	0.73 (0.63-0.84)	0.67 (0.55-0.78)	0.80 (0.71-0.89)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	Since the test is Procalcitonin which is a laboratory test, kappa was not calculated. We do not know if the PCT testing has changed in the 12 years since this study was performed or if different methods are available to determine the value.
Are the study results applicable to the patient in my practice?	Yes. The patient population is similar to the patient population at Bellevue, 88.5% non-white (although it does not divide this further). Their SBI rate was 13.3% which seems similar to the rate of SBI in other studies. They make no comment about immunization status which changes the risk of having an SBI and this study was performed after PCV 7 but before PCV 13 became available in 2010.
Will the results change my management strategy?	No. Currently practice varies by age. Febrile infants less than 3 months are screen with a UA and CBC. An LP, chest XRAY and stool culture are added as indicated. Infants > 3 months are variable screened for UTI and pneumonia as indicated. Routine screening for bacteremia and meningitis is no longer recommended in the well appearing febrile infant > 3 months or child. The baseline rate of SBI in this study was 13%. Using the predictive values for a Procalcitonin of > 0.5 ng/ml a patient with a positive Procalcitonin would have a risk of SBI of 46% while a patient with a negative Procalcitonin of 14%. A negative procalcitonin does not indicate a lower risk of SBI. A positive Procalcitonin indicates a 3 times risk of SBI but a UA has better test characteristics and a chest XRAY provides a definitive diagnosis.
Will patients be better off as a result of the test?	The authors have a wonderful statement in their discussion, “the availability of a biomarker that could accurately and rapidly identify SBI in febrile infants and children without obvious source would frequently obviate the need for invasive procedures such as lumbar punctures and reduce the use of empirical antibiotics and hospitalization and would be of significant importance to patients, their families and clinicians.” Unfortunately, Procalcitonin does not fit this bill. Although Procalcitonin did have better test characteristics than other available laboratory tests, and did have a higher area under the receiver operating characteristic curve and remain independently correlated with SBI in the regression analyses, given the potential outcome of death if SBI is missed, I don’t know how much it will help in limiting “invasive procedures.” In addition, the most common SBI in this study was urinary tract infection (60%) and a urinalysis had a sensitivity of 81.2% compared to 43.7% for Procalcitonin. Another 26% of SBI was due to pneumonia which may have been viral or bacterial.

CLINICAL BOTTOM LINE

BACKGROUND: It is important to identify potentially life threatening serious bacterial infections in infants and young children in order to prevent serious morbidity and mortality. There is currently no single test that can accurately predict SBIs in young febrile children. Procalcitonin has been shown to correlate with sepsis, severity of disease and mortality. It has been hypothesized that Procalcitonin may be a more accurate screening test than other traditional tests such as the WBC or ANC.

CLINICAL QUESTION: In well appearing, febrile infants and children (< 36 months) what are the test characteristics of Procalcitonin when compared to total WBC, absolute neutrophil count (ANC) and absolute band count (ABC) in identifying occult, serious bacterial infections (SBI)?

DESIGN/VALIDITY: This was a prospective cohort study of well appearing febrile children < 36-month old presenting to 4 hospitals that were otherwise being evaluated for SBI with laboratory tests including at least a blood culture. 226 patients were included in the primary analysis. There are a few validity concerns in the design of the study. They combine the 0-3-month age group (typically 'rule out sepsis') and the 3-36-month age (formerly 'rule out bacteremia"). These groups are known to have different epidemiology of serious bacterial infection. In fact, the authors used different fever cutoffs for these groups and no subgroup analysis was reported. Additionally, the extent of testing done to determine the outcome was at the examining physician's discretion creating the possibility of both selection bias (who was included) and verification bias (extent of laboratory evaluation).

PRIMARY RESULTS: The authors found that Procalcitonin had the most favorable predictive values, likelihood ratios and area under the curve when compared to the current standard laboratory tests of WBC count, ANC and ABC though there was no analysis to determine if there was a statistically significant difference in the test characteristics. Though Procalcitonin did not have the highest sensitivity and specificity it did have the best combination of sensitivity (53.3%) and specificity (90.1%). Only Procalcitonin and ANC remained independent predictors of SBI in the regression analysis. Procalcitonin had a significantly lower sensitivity than urinalysis for UTI which is the most common SBI (43.7% vs 81.2% respectively). A comparison to C-reactive protein, which has demonstrated better test characteristics in some studies than those commonly used, would have been helpful.

APPLICABILITY: This was a moderately large study sample which ultimately included only 30 patients with a serious bacterial infection. There are several concerns about the applicability of the results. The overall rate of SBI was about 13%, however, of those, almost 8% were UTI which can be evaluated with a UA and 3.5% with pneumonia which can be evaluated with chest XRAY. There was only a 1.7% rate of bacteremia, and only one child in the study had meningitis. In addition, the study was performed before the widespread use of PCV 13 so may represent a slightly different epidemiology then what is present in the current patient population. In addition, patients with acute otitis media (age not specified) who presumably would have been treated with antibiotics were included.

AUTHORS CONCLUSIONS: "Procalcitonin appears to be a more accurate marker than the white blood cell count, the absolute neutrophil count, or the absolute band count in identifying young febrile infants and children with serious bacterial infections. Further study on a larger cohort is required to more definitively determine the marginal benefit of procalcitonin over traditionally used screening laboratory tests in these patients."

POTENTIAL IMPACT: Although this study did demonstrate favorable test characteristics for Procalcitonin in identifying SBI, it still cannot be recommended as a screening tool for SBI in isolation. A clinical decision rule including a number of clinical and laboratory parameters would be helpful to determine the optimal clinical and laboratory and radiographic testing parameters to identify the rare febrile infant or child with an occult SBI.

FEBRILE NEONATE: BOSTON CRITERIA

In febrile neonates, 28-90 days, do history, physical examination and laboratory parameters ("Boston Criteria") accurately identify those at low risk for a serious bacterial infection who could be safely managed as outpatients with intramuscular Ceftriaxone?

Michael Mojica, M.D.
May 30, 2017

Baskin MN, O'Rourke EJ, Fleisher GR.

OUTPATIENT TREATMENT OF FEBRILE INFANTS 28 TO 89 DAYS OF AGE WITH INTRAMUSCULAR ADMINISTRATION OF CEFTRIAXONE.

J Pediatr. 1992 Jan;120(1):22-7.
PubMed ID; 1731019

STUDY DEFINITIONS	
POPULATION	Inclusion: 1. 28-90 days 2. Temperature ≥ 38 C 3. No antibiotics or DPT vaccine within 48 4. No allergies to Beta-lactams 5. Physical examination without ear, soft tissue, joint, or bone infection 6. Laboratory tests: CSF WBC < 10, Urinalysis: < 10 WBC/HPF OR dipstick negative for leukocyte esterase, 7. No infiltrate on chest radiograph (if obtained) 8. Peripheral leukocyte count < 20,000 9. Judged to not require admission for other than parenteral antibiotics: Normal vital signs for age and temperature, not ill appearing, not dehydrated, taking fluids 10. Cooperative and reliable parents available by telephone Exclusion: None specified Setting: Single Children's Hospital ED, 2/1987-4/1990
RULE	History: Gestational age, perinatal complications, previous antibiotics or vaccines Laboratory: Complete blood cell count, urinalysis, CSF analysis, and cultures of blood, urine (suprapubic aspiration or catheterization) and CSF. Acute Illness Observation Scale (See Appendix) Chest radiographs and stool cultures obtained at the discretion of treating MD Treatment: Ceftriaxone 50 mg/kg IM on days 1 and 2
REFERENCE STANDARD	Serious Bacterial Infection: Bacterial growth in from blood, CSF, urine, or Stool. Urinary tract infection: Urine culture with a single organism of > 1,000 colonies/ml (suprapubic) or > 10,000 colonies/ml (catheterization)
OUTCOME	Proportion with: Serious bacterial infection Subsequently admitted, Infection sequelae
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. The criteria included a comprehensive list of historical, examination and laboratory parameters.
Were all important predictors present in significant proportion of the study population?	Unclear. Data on the prevalence of each predictor used were not provided.
Were the outcome event and predictors clearly defined?	Yes. The outcome of serious bacterial infection was clearly defined. Some of the inclusion criteria are open to interpretation (e.g. physical examination findings, acute illness observation score, reliability of parents) and no measure of inter-rater reliability was presented.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Yes. The outcome of serious bacterial infection was defined by the presence of bacterial cultures. It is unclear if those reviewing the culture results were aware of the presence of the predictors though it is unlikely that knowledge of the predictors would influence the assessment of the outcome. Predictors were assessed prior the availability of culture results.
Was the sample size adequate (including an adequate number of outcome events)?	Unclear. The study included a total of 503 patients of which 27 (5.4%) had a serious bacterial infection.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

N = 503
336 (67%) 28-60 days
167 (33%) 61-89 days
SBI: 27 (5.4%):
Bacterial enteritis (2%)
UTI (1.6%)
Bacteremia without a UTI (1.6%)
Bacteremia with a UTI (0.2%)
Bacterial Meningitis (0%)

SBI versus no SBI
No significant difference in age, acute illness observation score or peripheral WBC in those with and without a SBI. Those with SBI had a statistically significant higher temperature (0.3 C), percentage bands (3.5%) and absolute band count (440) though differences were small and there was overlap in the standard deviations.

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

Of the patients meeting criteria for discharge with intramuscular ceftriaxone, 7.1% required subsequent admission. If the baseline rate of admission was 100% then implementation of the criteria could potentially reduce the admission rate by 93%.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

No. There was no internal statistical validation of the rule.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied?	☐ I ☐ II ☐ III ? ■ IV This is a difficult rule to classify. At best, it would be considered a level IV rule. Level IV rules have been derived only or validated only in split samples, large retrospective databases or by statistical methods. Level IV rules require further validation before they can be applied clinically. However, this rule was not statistically derived. The rule was instead assembled from potential predictors with predefined cutoffs. It may be unfair to apply the decision rule classification scheme to a study that pre-dated clear methodologic standards for clinical decision rules.
Does the rule make clinical sense?	Yes. Those without physical exam findings consistent with a bacterial infection and those with a normal urinalysis, normal CSF findings or those with normal biomarkers would be expected to have a lower risk of serious bacterial infection.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. The laboratory parameters should be reproducible. There was however, no measure of inter-rater reliability for the physical examination findings or for the components of acute illness observation score.
Is the rule applicable to the patients in my practice?	Likely Yes. The study population was from a single institution and demographic characteristics provided are limited to the age of the patients. The rate of serious bacterial infection in the study population is lower than that typically presented in the literature indicating that the criteria likely represent a low risk group.
Will the rule results change my management strategy?	Yes. The criteria provide a structure to the evaluation of the febrile neonate. This study demonstrated that outpatient management of febrile neonates with empiric antibiotics is feasible.
What are the benefits of applying the rule to my patients?	The potential benefits of applying the criteria is a reduction in admission for those at low risk of serious bacterial infection. This could reduce inpatient complications such as nosocomial infections.
What are the risks of applying the rule to my patients?	The primary risk is in sending home and treating with antibiotics a patient with a serious bacterial infection. None of the patients in study with a serious bacterial infection sustained a sequela of their infection though 1 patient with bacterial was found to have osteomyelitis on follow up. The patient was well appearing and not bacteremia on follow up.

CLINICAL BOTTOM LINE

BACKGROUND: At the time this study was published the standard practice was to complete a full sepsis evaluation and admit all febrile neonates less than 2-3 months of age for antibiotics pending culture results. Approximately 90% of infants who were admitted did not have a serious bacterial infection. Those admitted were at risk for nosocomial infections, complication such as intravenous catheter infiltration and antibiotic related adverse events. If a cohort of infants at very low risk of serious bacterial infection could be identified based on history, examination and laboratory findings available in a timely fashion in the emergency department then they could potentially benefit from fewer admissions.

CLINICAL QUESTION: In febrile neonates, 28-90 days, do history, physical examination and laboratory parameters (the “Boston Criteria”) accurately identify those at low risk for a serious bacterial infection who could be safely managed as outpatients with intramuscular Ceftriaxone?

DESIGN/RISK OF BIAS: This was a prospective cohort of 507 febrile neonates 28-90 days of age who met history, physical examination and laboratory criteria for outpatient management with intramuscular Ceftriaxone. 5.4% were subsequently determined to have a serious bacterial infection. Bacterial enteritis was the most common serious bacterial infection (2.0%) with bacteremia (1.8%) and urinary tract infection (1.8%). UTI is typically the most common serious bacterial infection in this population. There is the possibility of verification bias. 40.8% had a chest XRAY and catheterized or suprapubic urine was obtained in 95.2%

It would have been helpful to present the rate of serious bacterial infection in patients not meeting inclusion criteria to determine the test characteristics of the low risk criteria. For example, it is not possible to know the utility of including a lumbar puncture in these patients if those without meningitis are not included.

PRIMARY RESULTS: Clinical screening criteria did not discriminate between infants with and without serious bacterial infections. There was no statistically significant difference in age, acute illness observation score or peripheral WBC. Those with SBI had a statistically significant higher temperature (0.3 C), percentage bands (3.5%) and absolute band count (440) though differences were small and there was overlap in the standard deviations presented.

Of the patients meeting the inclusion criteria and were discharge on antibiotics 7.1% were subsequently admitted. If all infants were previously admitted this would results in a potential decreased in the rate of admission by 93%.

APPLICABILITY: The study population was from a single institution and demographic characteristics provided are limited to the age of the patients. Though the majority of the criteria were objective laboratory measure the Inter-rater reliability for physical examination findings and the acute illness observation score were not presented. 2.0% of the patients with a serious bacterial infection had bacterial enteritis. This is considerable higher that other studies. In addition, 97.3% of the serious bacterial infections were susceptible to Ceftriaxone. This may not be true today.

This is a difficult rule to classify. At best, it would be considered a level IV rule. Level IV rules have been derived only or validated only in split samples, large retrospective databases or by statistical methods. Level IV rules require further validation before they can be applied clinically. However, this rule was not statistically derived. The rule was instead assembled from potential predictors with predefined cutoffs. It may be unfair to apply the rule classification scheme to a study that pre-dated clear methodologic standards for clinical decision rules.

AUTHOR'S CONCLUSION: "We conclude that outpatient management with intramuscular administration of ceftriaxone, after a full evaluation for sepsis and with adherence to a strict follow-up protocol, is a safe alternative to hospital admission for these infants."

POTENTIAL IMPACT: The Boston criteria provide a structured approach to the evaluation of the febrile neonate. This study demonstrated that outpatient management of febrile neonates with empiric antibiotics is feasible. The potential benefits of applying the Boston Criteria is a reduction in admission for those at low risk of serious bacterial infection. This could reduce inpatient complications such as nosocomial infection.

APPENDIX: BOSTON CRITERIA

BOSTON CRITERIA
Age 28-90 days
Temperature > 38.0 C (rectally in ED or a parental history of an equivalent rectal temperature)
Physical examination: No ear, soft tissue, joint, or bone infection
No source of infection identified on initial screening laboratory tests:
CSF WBC < 10
Urinalysis: < 10 WBC/HPF OR dipstick negative for leukocyte esterase
No infiltrate on chest radiograph (if obtained)
Peripheral leukocyte count < 20,000
Judged not to require admission to the hospital for other than parenteral antibiotics
Vital signs in the normal range for age and temperature
Not ill appearing
Not dehydrated
Taking fluids
Cooperative and reliable parents
Caregiver available by telephone
No antimicrobial agents received within the preceding 48 hours
No allergies to Beta-lactam antimicrobial agents
No immunization with diphtheria and tetanus toxoids and pertussis vaccine within 48 hours

APPENDIX: CLINICAL DECISION RULES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

APPENDIX: ACUTE ILLNESS OBSERVATION SCORE

ACUTE ILLNESS OBSERVATION SCORE (FEBRILE CHILDREN 3-36 MONTHS)	
QUALITY OF CRY	
Strong or no cry	1
Whimper or sob	3
Weak cry, moan, or high pitched cry	5
REACTION TO PARENTS	
Brief cry or content	1
Cries off and on	3
Persistent cry	5
STATE VARIATION	
Awakens quickly	1
Difficult to awaken	3
No arousal or falls asleep	5
COLOR	
Pink (1 point)	1
Acrocyanosis	3
Pale, cyanotic, or mottled	5
HYDRATION	
Eyes, skin, and mucus membranes moist	1
Mouth slightly dry	3
Mucus membranes dry, eyes sunken	5
SOCIAL RESPONSE	
Alert or smiles	1
Alert or brief smile	3
No smile, anxious, or dull	5
TOTAL SCORE	
Score > 10 is considered high risk for serious illness	

McCarthy PL, Lembo RM, Fink HD, Baron MA, Cicchetti DV.
Observation, History, and Physical Examination in Diagnosis of Serious Illnesses in Febrile Children Less Than or Equal to 24 Months.
J Pediatr. 1987 Jan;110(1):26-30., PubMed ID: 3540248

FEBRILE NEONATE:
CBC ACCURACY FOR INVASIVE INFECTIONS

In non-critically ill febrile neonates less than or equal to 60 days of age what is the diagnostic accuracy of CBC components (Total White Blood Cell (WBC) count, Absolute Neutrophil Count (ANC) and Platelet count) in identifying those with and without an invasive bacterial infection (Bacteremia and/or Meningitis)?

September 2017

Michael Mojica

Cruz AT, Mahajan P, Bonsu BK, Bennett JE, Levine DA, Alpern ER, Nigrovic LE, Atabaki SM, Cohen DM, VanBuren JM, Ramilo O, Kuppermann N; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network.

ACCURACY OF COMPLETE BLOOD CELL COUNTS TO IDENTIFY FEBRILE INFANTS 60 DAYS OR YOUNGER WITH INVASIVE BACTERIAL INFECTIONS.

JAMA Pediatr. 2017 Sep 11: e172927.
PubMed ID: 28892537

STUDY DEFINITIONS	
POPULATION	Inclusion: ≤ 60 days, temperature ≥ 38°C, blood cultures obtained, cerebrospinal fluid (CSF) cultures obtained or telephone follow-up within 7 days of ED visit. Infants with urinary tract infections and bacteremia and/or bacterial meningitis were included. Exclusion: • Critically ill: Requiring emergent interventions such as intubation, use of vasoactive medications or cardiopulmonary resuscitation • Premature: Gestational age < 37 weeks • Antibiotics within 4 days prior to ED visit • Major congenital malformations or comorbid medical conditions: Inborn errors of metabolism, congenital heart disease, chronic lung disease, immunosuppression or immune-deficiencies, or indwelling catheters or shunts. • Previously enrolled infants • Infants for whom the presence of bacteremia or meningitis was unknown. • CBC components missing • Febrile infants with urinary tract infections without invasive bacterial infection. Setting: 26 Pediatric Hospital EDs in the Pediatric Emergency Care Applied Research Network. 2008-2013.
TEST	Leukocytosis: WBC count ≥ 15,000 cells/μL Leukopenia: WBC count < 5,000 cells/μL Neutrophilia: ANC > 10,000 cells/μL (Above thresholds based-on use by existing algorithms, Band counts not consistently available) Thrombocytosis: Platelets ≥ 450 × 10^3 cells/μL Thrombocytopenia: Platelets < 100 x 10^3 cells/μL or < 150 x 10^3 cells/μL
REFERENCE STANDARD	Invasive Bacterial Infection: Bacteremia and/or Bacterial Meningitis Bacteremia: Blood culture with growth of a single pathogen. Bacterial Meningitis: CSF culture with growth of a single pathogen Contaminants: *Bacillus* non-*cereus*/non-*anthracis*, diphtheroids, *Lactobacillus*, *Micrococcus*, coagulase-negative staphylococci, and viridans group streptococci.
OUTCOME	Test Characteristics at predefined cutoffs Area under the receiver operating characteristic curve and test optimal cut-off.
DESIGN	Prospective Cohort (Planned secondary analysis)

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Unclear. Patients were febrile neonates at risk for invasive bacterial infection. Critically ill infants were excluded based on the need for critical care interventions (intubation, cardiopulmonary resuscitation, vasoactive infusions). This leaves room for patients who are ill appearing (respiratory distress, altered mental status, signs of poor perfusion) but not requiring those interventions to be included in the study population. Laboratory screening to identify those at low risk of invasive bacterial infection is most useful in those who are well appearing. The proportion of infants who were ill appearing but not requiring critical care interventions was not presented.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The reference standard was a single bacterial pathogen identified on blood or CSF culture. Bacterial contaminants were pre-defined. All patients had a blood culture. 75.5% had an LP attempted and the LP was successful in 98.2%. Therefore 26.3% did not have a CSF culture. The proportion of those who did not have an LP who were treated with antibiotics was not presented.
Were those interpreting the test and reference standard blind to the other results?	Unclear. Those assessing the CBC parameters were temporally blinded to the presence of an invasive bacterial infection defined by culture results. It is unclear if those assessing the culture results were aware of the CBC parameters. As both the tests and reference standard are objective laboratory results it is unlikely that lack of blinding, could bias assessment.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	Yes and No. Inclusion required that all patients had a blood culture sent. The presence of bacterial meningitis was defined as CSF culture with a single pathogen or clinical follow up within 7 days. The proportion of patient who did not have a CSF culture who were available for follow up was not presented.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 4,313
LP: Attempt (75.8%), Successful (98.2%)
Age: 0-28 days (31%)
Disposition: Admitted (74%)

Invasive Bacterial Infection:
0-60 days: 2.2% (97/4,313), 95% CI (1.8, 2.7%)
≤ 28 days: 4.3% (57/1,340), 95% CI (3.2, 5.3%)
29 to 60 days: 1.4% (40/2,973), 95% CI (1.0, 1.8%)

Isolated Bacteremia: 1.7% (73/4,313), 95% CI (1.4, 2.1%)
Bacterial Meningitis: 0.6%, (24/4,313), 95% CI (0.4, 0.8%), 46% (11/24) also had bacteremia

PATHOGENS

BACTEREMIA	MENINGITIS	E COLI	GBS	OTHER
YES	NO	43.8%	19.2%	Staph Aureus: 15.1%
NO	YES	23.1%	23.1%	Enterococcus: 23.1%
YES	YES	9.1%	54.6%	4 others with 9.1%

TEST CHARACTERISTICS AT PREDEFINED CUTOFFS*

TEST	SN	SP	PV (+)	PV (-)	LR (+)	LR (-)
WBC < 5K	10% (4, 16)	91% (90, 92)	3% (1, 4)	98% (97, 98)	1.1 (0.6, 2.1)	1 (0.9, 1.1)
WBC ≥ 15K	27% (18, 36)	87% (86, 88)	5% (3, 6)	98% (98, 99)	2.1 (1.5, 2.9)	0.8 (0.7, 1.0)
< 5 or ≥ 15k	37% (27, 47)	78% (77, 79)	4% (3.5)	98% (98, 99)	1.7 (1.3, 2.2)	0.8 (0.7, 0.9)
ANC ≥ 10K	18% (10, 25)	96% (96, 97)	9% (5, 14)	98% (98, 99)	4.5 (2.9, 7.2)	0.9 (0.9, 1.0)
PLAT < 100	7% (2, 12)	100% (99, 100)	26% (9, 42)	98% (97, 98)	15.1 (6.6, 34.9)	0.9 (0.9, 1.0)
PLAT < 150	9% (4, 15)	99% (99, 99)	16% (6, 25)	98% (97, 98)	7.9 (4.0, 15.7)	0.9 (0.9, 1.0)

*Cutoffs based on those typically used in existing algorithms

TEST CHARACTERISTICS AT OPTIMAL CUTOFFS*

TEST	SN	SP	PV (+)	PV (-)	LR (+)	LR (-)
WBC≥ 11.6	48% (39, 58)	68% (66, 69)	3% (2, 4)	98% (98, 99)	1.5 (1.2, 1.9)	0.8 (0.6, 0.9)
ANC ≥ 4.1	67% (58,76)	67 (66, 69)	4% (3, 5)	99% (99, 99)	2.0 (1.8, 2.4)	0.5 (0.4, 0.7)
PLAT ≤ 362	61% (51, 71)	56% (55, 58)	3% (2,4%)	98% (98, 99)	1.4 (1.2, 1.7)	0.7 (0.5, 0.9)

*Cutoffs derived from ROC curves

AREA UNDER THE RECEIVER OPERATING CHARACTERISTIC CURVE			
	0-28 DAYS	29-60 DAYS	0-60 DAYS (ALL)
WBC	0.57 (0.48. 0.66)	0.52 (0.42, 0.62)	0.57 (0.50, 0.63)
ANC	0.73 (0.66, 0.80)	0.60 (0.50, 0.70)	0.70 (0.64, 0.76)
PLATELETS	0.56 (0.48, 0.65)	0.62 (0.53, 0.71)	0.61 (0.55, 0.67)
Accuracy: AUC: < 0.7 poor, 0.7-0.8 minimally, 0.8-0.9 good, > 0.9 excellent			

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Yes. The tests in this study are objective laboratory results. There should not be a concern for reproducibility.
Are the study results applicable to the patients in my practice?	Yes. We see a number of febrile infants at our sites who are likely similar to the study population enrolled. However, the patients in the study appear to be a somewhat high-risk population. The 76% who had an LP attempted seems high given that only 31% of patients were less than 28 days. Also, the admission rate of 74% seems high. Ill appearing patients who did not require critical care interventions may also have been included. The CBC parameters are of less value in ill appearing patients where the decision to admit and treat is already defined.
Will the test results change my management strategy?	Possibly. The CBC alone is never the only factor in decision making in the febrile neonate. It is possible that the CBC parameters will play a smaller role in future decision making. However, until alternate approaches (CRP, Procalcitonin, novel biomarkers) are both readily available at the time of decision making and have been conclusively studied, there is nothing to replace the CBC. It would have been helpful to present the test characteristics of the CBC parameters as part of a clinical decision rule taking into account historical risk factors, vital signs, physical examination findings and results of the urinalysis and viral testing.
Will patients be better off as a result of the test?	Unlikely. The discriminatory ability of the CBC parameters studied is poor. The priority in identifying a disease process with high risk of consequences if missed is a high sensitivity. The highest sensitivity of the currently recommend CBC parameters was the 27% for a WBC < 5,000 or ≥ 15,000. The highest sensitivity of the derived CBC parameter cutoffs was 67% for a ANC > 4,100

CLINICAL BOTTOM LINE

BACKGROUND: The management of the febrile neonate remains an area of considerable debate. Despite multiple published decision rules (Rochester, Boston and Philadelphia criteria), variability exists in the evaluation and management of these patients. As the epidemiology of serious bacterial infection has evolved primarily due to vaccination for H influenzae and S Pneumoniae and with the availability of new biomarkers, alternative approaches should be evaluated. The components of the CBC have traditionally been used to risk stratify febrile neonate into low-risk and not low-risk groups. The accuracy of CBC components should be re-assessed as the epidemiology of serious and invasive bacterial infections evolve.

CLINICAL QUESTION: In non-critically ill febrile neonates less than or equal to 60 days of age what is the diagnostic accuracy of CBC components (Total White Blood Cell (WBC) count, Absolute neutrophil count (ANC) and Platelet count) in identifying those with and without an invasive bacterial infection (Bacteremia and/or Meningitis)?

DESIGN/RISK OF BIAS: This was a well-designed, preplanned secondary analysis of a prospective enrolled population of febrile neonates at Children's hospital ED's in the PECARN network. The study included 4,313 febrile neonates for which a blood culture was obtained. Bacterial meningitis was assessed by CSF culture or clinical followed. The accuracy of CBC parameters (WBC, ANC and platelet count) was assessed both as test characteristics at commonly used cutoff values or for the test as a whole by the area under the receiver operating characteristic curve in determining the presence of absence of invasive bacterial infections (bacteremia and/or bacterial meningitis).

In the 26.3% patients who did not have a CSF culture obtain the proportion who received antibiotics and the proportion available for follow up was not presented. In addition, the CBC is just one piece of the evaluation of the febrile neonate. It would have been helpful to present the test characteristic for those with and without an abnormal urinalysis or to derive a clinical decision rule using the other factors typically included in decision making.

PRIMARY RESULTS: Invasive Bacterial Infection occurred in 2.2%, 95% CI (1.8, 2.7%) of those 0-60 days, 4.3%, 95% CI (3.2, 5.3%) of those ≤ 28 days and 1.4%, 95% CI (1.0, 1.8%) of those 29 to 60 days. Isolated Bacteremia occurred in 1.7%, 95% CI (1.4, 2.1%) of patients. Bacterial Meningitis occurred in 0.6%, 95% CI (0.4, 0.8%). 46% of those with bacterial meningitis also had bacteremia.

No single CBC parameter at either existing or newly derived test thresholds had both an adequate sensitivity and specificity to distinguish between those with and without invasive bacterial infection. For example, the commonly used WBC > 15,000 had a Sensitivity of 27%, 95% CI (18, 36%) and Specificity of 87%, 95% CI (86, 88%). Discriminatory ability for each parameter was poor as defined by an area under a receiver operating characteristic curve of < 0.7. CBC: AUC = 0.57, 95% CI (0.50, 0.63), ANC: AUC = 0.70, 95% CI (0.64, 0.76), Platelet Count: AUC = 0.61, 95% CI (0.55, 0.67). The discriminatory ability did not improve when the population was analyzed as a subgroup with age categories of 0-28 days and 29-60 days.

TEST CHARACTERISTICS AT PREDEFINED CUTOFFS						
TEST	SN	SP	PV (+)	PV (-)	LR (+)	LR (-)
WBC < 5K	10% (4, 16)	91% (90, 92)	3% (1, 4)	98% (97, 98)	1.1 (0.6, 2.1)	1 (0.9, 1.1)
WBC ≥ 15K	27% (18, 36)	87% (86, 88)	5% (3, 6)	98% (98, 99)	2.1 (1.5, 2.9)	0.8 (0.7, 1.0)
< 5 or ≥ 15k	37% (27, 47)	78% (77, 79)	4% (3.5)	98% (98, 99)	1.7 (1.3, 2.2)	0.8 (0.7, 0.9)
ANC ≥ 10K	18% (10, 25)	96% (96, 97)	9% (5, 14)	98% (98, 99)	4.5 (2.9, 7.2)	0.9 (0.9, 1.0)
PLAT < 100	7% (2, 12)	100% (99, 100)	26% (9, 42)	98% (97, 98)	15.1 (6.6, 34.9)	0.9 (0.9, 1.0)
PLAT < 150	9% (4, 15)	99% (99, 99)	16% (6, 25)	98% (97, 98)	7.9 (4.0, 15.7)	0.9 (0.9, 1.0)

AREA UNDER THE RECEIVER OPERATING CHARACTERISTIC CURVE			
	0-28 DAYS	29-60 DAYS	0-60 DAYS (All)
WBC	0.57 (0.48. 0.66)	0.52 (0.42, 0.62)	0.57 (0.50, 0.63)
ANC	0.73 (0.66, 0.80)	0.60 (0.50, 0.70)	0.70 (0.64, 0.76)
PLATELETS	0.56 (0.48, 0.65)	0.62 (0.53, 0.71)	0.61 (0.55, 0.67)

APPLICABILITY: This was a multicenter study including patients at children's hospital emergency departments. There is no reason to believe that the study's results would not be applicable to community hospital ED's. In addition, the rate of invasive bacterial infection and the pathogens involved is similar to many recent studies. However, the patient population may represent a particularly high-risk group. The inclusion of only patients who had a blood culture sent may result in spectrum bias. In addition, the 76% who had an LP attempted seems high given that only 31% of patients were less than 28 days. Also, the admission rate of 74% seems high. In addition, ill appearing patients who did not require critical care interventions may have been included. The CBC parameters are of less value in ill appearing patients where the decision to admit and treat is already defined.

AUTHOR'S CONCLUSION: "Complete blood cell count parameters had poor accuracy in distinguishing febrile infants 60 days and younger with and without invasive bacterial infections in the post pneumococcal conjugate vaccine era, although the ANC had the highest sensitivity. Physicians who use CBC thresholds in an attempt to risk stratify febrile young infants may be falsely reassured by normal CBC parameters. When used in isolation, either at commonly used thresholds or at the optimal thresholds identified here, CBC parameters have at best modest discriminatory ability. In an era where better screening tests exist to identify infants with IBIs, we need to question our continual reliance on a test whose greatest strength may simply be in its ready availability in clinical practice."

POTENTIAL IMPACT: The discriminatory ability of the CBC parameters studied is poor. The priority in identifying a disease process with high consequences if missed is a high sensitivity. The highest sensitivity of the currently recommended CBC parameters was 27% for a WBC < 5K or ≥ 15K.

The CBC alone is never the only factor in decision making in the febrile neonate. It is possible that the CBC parameters will play a lesser role in future evaluations. However, until alternate approaches (CRP, Procalcitonin, novel biomarkers) are both readily available at the time of decision making and conclusively studied, there is nothing to replace the CBC. It would have been helpful to present the test characteristics of the CBC parameters as part of a clinical decision rule taking into account historical risk factors, vital signs, physical examination findings and results of the urinalysis and viral testing.

Finally, 15% of bacteremia was due to Staph aureus. This may require a reconsideration of the traditional antibiotic selection, such as Ampicillin and Cefotaxime, in this population to provide coverage of Methicillin-Resistant Staph Aureus.

FEBRILE NEONATE:
PECARN DECISION RULE

In febrile neonates less than 60 days of age,
do clinical and laboratory parameters
adequately identify those at low risk
for serious bacterial infection?

Michael Mojica, MD
February 2019

Kuppermann N, Dayan PS, Levine DA, Vitale M, Tzimenatos L, Tunik MG, Saunders M, Ruddy RM, Roosevelt G, Rogers AJ, Powell EC, Nigrovic LE, Muenzer J, Linakis JG, Grisanti K, Jaffe DM, Hoyle JD Jr, Greenberg R, Gattu R, Cruz AT, Crain EF, Cohen DM, Brayer A, Borgialli D, Bonsu B, Browne L, Blumberg S, Bennett JE, Atabaki SM, Anders J, Alpern ER, Miller B, Casper TC, Dean JM, Ramilo O, Mahajan P: Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN).

A CLINICAL PREDICTION RULE TO IDENTIFY
FEBRILE INFANTS 60 DAYS AND YOUNGER
AT LOW RISK FOR SERIOUS BACTERIAL INFECTIONS

JAMA Pediatr. 2019 Apr 1;173(4):342-351.
PubMed ID: 30776077

STUDY DEFINITIONS	
POPULATION	Inclusion: Infants < 60 days with fever (≥ 38 C rectally) within 24 hours of ED visit Fever in the ED, prior healthcare setting or at home Exclusion: Critically ill Premature (36 weeks' gestation) Preexisting medical conditions Indwelling devices Soft tissue infections Setting: 22 Emergency Departments in the PECARN Network, 3/2011-5/2013
RULE PARAMETERS	Age group (≤ 28 days vs > 28 days) Temperature Duration of fever Yale Observation Score (See Appendix) Clinical suspicion of SBI (< 1%, 1-5%, 6-10%, 11-50%, >50%) prior to lab results *Urinalysis (+) Leukocyte esterase OR (+) Nitrite OR Pyuria (>5 WBC/HPF) WBC count *Absolute neutrophil count (ANC) *Serum procalcitonin level (PCT) (*Included in the Decision Rule as independent predictors of SBI)
REFERENCE STANDARD	Serious Bacterial Infection (SBI) (≥ 1 of the following) 1. Bacterial Meningitis: Growth of a single pathogen in the CSF 2. Bacteremia: Growth of a single pathogen in the blood 3. UTI: Growth of single pathogen with: a. ≥ 1,000 CFU/ml (suprapubic aspiration) OR b. ≥ 50,000 CFU/ml (catherization) OR c. 10,000-50,000 CFU/ml (catherization) with an abnormal urinalysis ((+) leukocyte esterase OR (+) nitrites OR pyuria (> 5 WBC/HPF)
OUTCOME	Rule Characteristics: All SBI
DESIGN	Observational: Prospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. Patient demographic factors, vitals signs, clinical appearance and laboratory parameters were included in the derivation process. Viral testing was not included as it was not available at all sites in a timely manner.
Were all important predictors present in significant proportion of the study population?	Yes. It appears that predictors were present in a significant portion of the population. However, the median YOS was 6 (range 6-10) and only 6% of patients had clinical suspicion of SBI in the 11-50% and the > 50% categories.
Were the outcome event and predictors clearly defined?	Yes. Clear definitions of each of the predictors and the serious bacterial infection outcomes were provided.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Yes. Assessment of the predictors occurred prior to the determination of the outcome. It is unclear if outcomes assessors were aware of the predictors. However, it is unlikely that knowledge of the predictors would influence the interpretation of the objective definitions of serious bacterial infection.
Was the sample size adequate (including an adequate number of outcome events)?	Unclear. There is no clear standard for sample size determination in recursive partitioning. For logistic regression, it is generally desired to have 10 outcomes for each of the predictor variables. This rule has 3 predictors and included 170 patients with a serious bacterial infection (56 outcomes per predictor)

WHAT ARE THE RESULTS?

DEMOGRAPHIC DATA

< 60 days: n = 1,821 (combined derivation and validation sets)
(28 days: n = 555/1,821(30.5%), 29-60 days: n = 1,266/1,821 (69.5%))
SBI: 9.3%, 95% CI (8.1, 10.8%)
UTI: 8.3%, 95% CI (7.1, 9.6%)
Bacteremia: 1.4%, 95% CI (1.0, 2.1%)
Bacterial Meningitis: 0.5%, 95% CI (0.3, 1.0%)
Most common pathogens: E Coli (73.8%), Group B Strep (7%)

LABORATORY ASSESSMENT (COMBINED DERIVATION AND VALIDATION SETS)

Urinalysis	99.2% (1,806/1,821)	Urine culture	100% (1,821/1,821)
Complete Blood Count	97.5% (1,775/1,821)	Blood culture	100% (1,821/1,821)
Procalcitonin	100% (1,821/1,821)		
Lumbar puncture	76.8% (1,399/1,821)	CSF culture	76% (1,383/1,821)

SERIOUS BACTERIAL INFECTION (COMBINED DERIVATION AND VALIDATION SETS)

	0-60 days	28 days	29-60 days
UTI*	8.3% (151/1,821)	11.2% (62/555)	7% (89/1,266)
Bacteremia*	1.4% (26/1,821)	2.2% (12/555)	1.1% (14/1,266)
Bacterial Meningitis*	0.5% (10/1,821)	1.3% (7/555)	0.2% (3/1,266)
ANY SBI*	9.3% (170/1,821)	13% (72/555)	7.7% (98/1,266)
*Includes patients with more than 1 SBI (e.g. UTI + Bacteremia)			

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SENSITIVITY AND PREDICTIVE VALUE OF A NEGATIVE RULE WITH 95% CONFIDENCE INTERVALS)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SPECIFICITY AND PREDICTIVE VALUE OF A POSITIVE RULE WITH 95% CONFIDENCE INTERVALS)

Univariate Predictors of SBI: 28 days, ↑ Temperature, ↑ WBC, ↑ ANC, ↑ Procalcitonin, higher clinician suspicion (Table 2)

Recursive Partitioning: Independent Predictors of SBI:
Positive Rule = (+) Urinalysis OR ANC > 4,090 per microL OR PCT > 1.7 ng/ml
Negative Rule = (-) Urinalysis AND ANC 4,090 per microL AND PCT 1.7 ng/ml

DERIVATION SET				
		Serious Bacterial Infection		
		YES	NO	
RULE	POSITIVE	81	305	386
	NEGATIVE	1	521	522
		82	826	908

RULE CHARACTERISTICS	CALCULATION	POINT ESTIMATE (95% CI)
Prevalence	82/908	9.0% (7.3, 11.1%)
Sensitivity	81/82	98.8% (92.5, 99.9%)
Specificity	521/826	63.1% (59.7, 66.4%)
Predictive Value (+) Test	81/386	21.0% (17.1, 25.5%)
Predictive Value (-) Test	521/522	99.8% (98.8, 100%)
Likelihood Ratio (+) Test	(81/82)/(305/826)	2.68 (2.44, 2.93)
Likelihood Ratio (-) Test	(1/82)/(521/826)	0.02 (0.003, 0.14)

In the derivation group, the rule divided a group of patients with a 9% risk of SBI into a high-risk group with an SBI rate of 21.0% (PPV) if the rule was positive and a low-risk group with an SBI rate of 0.2% (1-NPV) if the rule was negative.

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

In the combined derivation and validation sets, 56% of patients were classified as low risk for SBI. 76% of the infants in the study underwent an LP. The LP rate could be reduced by 20% (76% - 56%) if low risk infants did not have an LP. Antibiotic use and hospital admission could potentially be reduced to the same extent though the baseline rate of use these were not reported in order to calculate the proportion with a potential reduction in resource utilization.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

There was an internal statistical validation of the decision rule using split data sets. Patients (n=1,821) were randomized to either the derivation set (n=908) or the validation set (n=913). Randomization was constrained to ensure equal numbers of the serious bacterial infections in each of the data sets. Test characteristics for the validation and derivation sets were very similar.

VALIDATION SET				
		Serious Bacterial Infection		
		YES	NO	
RULE	POSITIVE	86	330	416
	NEGATIVE	2	495	497
		88	825	913

RULE CHARACTERISTICS	CALCULATION	POINT ESTIMATE (95% CI)
Prevalence	88/913	9.6% (7.9, 11.7%)
Sensitivity	86/88	97.7% (91.3, 99.6%)
Specificity	495/825	60.0% (56.6, 63.3%)
Predictive Value (+) Test	86/416	20.7% (16.9, 25.0%)
Predictive Value (-) Test	495/497	99.6% (98.4, 99.9%)
Likelihood Ratio (+) Test	(86/88)/(330/825)	2.44 (2.23, 2.67)
Likelihood Ratio (-) Test	(2/88)/(495/825)	0.04 (0.01, 0.15)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (See Appendix)	☐ I ☐ II ☐ III ■ IV This is a level IV clinical decision rule. It has been derived only or validated only in split samples, large retrospective databases or by statistical methods. Level IV decision rules require further validation before they can be applied clinically.
Does the rule make clinical sense?	Yes, the rule makes sense. The urinalysis identifies UTI which is the most common SBI in the population. The ANC and PCT are acute phase reactants that are more likely to be elevated in the presence of an SBI.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Yes. The parameters in rule (UA, ANC and PCT) are objective laboratory tests which are not open to interpretation. The procalcitonin results would need be available in a time frame to influence clinical decision making. The PCT results were not available to clinicians in this study.
Is the rule applicable to the patients in my practice?	Yes. The population included febrile neonate in 22 pediatric emergency departments in the US likely making the results generalizable to patients meeting the inclusion and exclusion criteria in the ED setting. The 9.3% rate of SBI is similar to that commonly reported in the literature.
Will the rule results change my management strategy?	As always, this depends on what your management strategy is to begin with. I would like not to have to perform a lumbar puncture on all infants < 28 days of age.
What are the benefits of applying the rule to my patients?	The rule has the potential to decrease the rate of lumbar puncture, unnecessary antibiotics and hospital admission in patients who meet low risk criteria.
What are the risks of applying the rule to my patients?	The major risk of using the rule would be the possibility of missing a patient with an SBI. In the derivation set 0.2%, 95% CI (0, 1.1%) of the patients who met low risk criteria had an SBI. 1 patient with bacteremia was missed in the derivation set. 2 patients (0.4%, 95% CI (0.1, 1.6%) with a UTI only (and negative UA) were missed in the validation set.

CLINICAL BOTTOM LINE

BACKGROUND: The management of the febrile neonate remains an area of considerable debate. Despite multiple published decision rules (Rochester, Boston and Philadelphia criteria), variability exists in the evaluation and management of these patients. Those frequently referenced criteria used laboratory cutoffs that were not statistically derived.

As the epidemiology of serious bacterial infection has evolved primarily due to vaccination for H influenzae and S Pneumoniae and with the availability of new biomarkers, alternative approaches should be evaluated. The ability to identify a subgroup of febrile neonates at low risk for serious bacterial infection could potentially reduce the frequency of lumbar puncture, antibiotic administration and admission for these patients. This should be balanced by the risk of missed serious bacterial infections with the potential for serious morbidity and mortality.

CLINICAL QUESTION: In febrile neonates less than 60 days of age, do clinical and laboratory parameters adequately identify those at low risk for serious bacterial infection?

DESIGN/RISK OF BIAS: This is a well-designed, prospective cohort of febrile neonates less than 60 days of age that were enrolled in 22 pediatric Emergency Departments in the PECARN network. Patients were a convenience sample who presented when research staff were available indicating the possibility of selection bias. However, the rate of SBI in the study is similar to that commonly found in the medical literature.

The goal of the study was to identify parameters the identify infants at low risk for serious bacterial infection. Patient demographic factors, vital signs, clinical appearance and laboratory parameters were included in the derivation process. Viral testing was not included as it was not available at all sites in a timely manner. 24% (n=438) of infants did not have a CSF culture indicating the possibility of verification bias. No patients without a CSF culture were subsequently found to have bacterial meningitis on follow-up (observation in hospital (n=216), phone follow-up (n=216), medical record review (n=178). It is possible that those with follow-up by medical record review did not return to the same hospital. Assessment of the predictors occurred prior to the determination of the outcome. It is unclear if outcomes assessors were aware of the predictors. However, it is unlikely that knowledge of the predictors would influence the interpretation of the objective definitions of serious bacterial infection.

The primary outcome was the accuracy of the decision rules in identifying those with and without serious bacterial infection. SBI was defined as the presence of a UTI, bacteremia or bacterial meningitis or any combination of the three.

PRIMARY RESULTS: The study included 1,821 febrile neonates less than 60days (28 days (30.5%), 29-60 days (69.5%)). A serious bacterial infection occurred in 9.3%, 95% CI (8.1, 10.8%), UTI: 8.3%, 95% CI (7.1, 9.6%), bacteremia: 1.4%, 95% CI (1.0, 2.1%) and bacterial meningitis: 0.5%, 95% CI (0.3, 1.0%). However, only 30 patients with bacteremia or bacterial meningitis were included limiting the conclusions that can be made regarding these serious bacterial infections.

The rule parameters were derived and validated in split sets using recursive partitioning. Three independent predictors of serious bacterial infection were identified: UA, ANC and PCT (Table below).

PECARN FEBRILE NEONATE DECISION RULE: LOW RISK CRITERIA*
(-) Urinalysis = (-) Leukocyte esterase AND (-) Nitrite, AND Absence of Pyuria (5 WBC/HPF)
ANC 4,090 per microL (to convert to $\times 10^9$ per liter, multiply by 0.001)
PCT 1.7 ng/ml
*All 3 criteria need to be fulfilled in order for the patient to be consider low risk by the rule The authors report a similar sensitivity but lower specificity with rounded values of ANC 4,000 and PCT 1.5 (see supplementary materials)

There was an internal statistical validation of the decision rule using split data sets. Patients were randomized to either the derivation set (n=908) or the validation set (n=913). Test characteristics for the validation and derivation sets were very similar.

The rule divided a group of patients (derivation set) with a 9.0% risk of SBI into a high-risk group with an SBI rate of 21.0% (PPV) if the rule was positive and a low-risk group with an SBI rate of 0.2% (1-NPV) if the rule was negative. 1 patient with bacteremia was missed in the derivation set. 2 patients with a UTI (and a negative UA) were missed in the validation set.

RULE CHARACTERISTICS	DERIVATION	VALIDATION
Prevalence	9.0% (7.3, 11.1%)	9.6% (7.9, 11.7%)
Sensitivity	98.8% (92.5, 99.9%)	97.7% (91.3, 99.6%)
Specificity	63.1% (59.7, 66.4%)	60.0% (56.6, 63.3%)
Predictive Value (+) Test	21.0% (17.1, 25.5%)	20.7% (16.9, 25.0%)
Predictive Value (-) Test	99.8% (98.8, 100%)	99.6% (98.4, 99.9%)
Likelihood Ratio (+) Test	2.68 (2.44, 2.93)	2.44 (2.23, 2.67)
Likelihood Ratio (-) Test	0.02 (0.003, 0.14)	0.04 (0.01, 0.15)

In the combined derivation and validation sets, 56% of patients were classified as low risk for SBI. 76% of the infants in the study underwent an LP. The LP rate could be reduced by 20% (76% - 56%) if low risk infants did not have an LP. Antibiotic use and hospital admission could potentially be reduced to the same extent though the baseline rate of use these were not reported in order to calculate the proportion with a potential reduction in resource utilization.

APPLICABILITY: The population included febrile neonate in 22 pediatric emergency departments from around the U.S. likely making the results generalizable to patients meeting the study's inclusion and exclusion criteria in the ED setting. A 9.3% rate of SBI (combined data sets) is similar to that commonly reported in the literature.

This is a level IV clinical decision rule. It has been derived only or validated only in split samples, large retrospective databases or by statistical methods. Level IV decision rules require further validation before they can be applied clinically.

AUTHOR'S CONCLUSION: "We derived and validated an accurate prediction rule to identify febrile infants 60 days and younger at low risk for SBIs using 3 easily obtainable, objective variables: the urinalysis, the ANC, and serum procalcitonin. Once further validated, implementation of the rule has the potential to substantially decrease the use of lumbar punctures, broad-spectrum antibiotics, and hospitalization for many febrile infants 60 days and younger."

POTENTIAL IMPACT: This is a simple rule with 3 objective laboratory criteria. If validated broadly, the rule has the potential to decrease the rates of lumbar puncture, unnecessary antibiotics and hospital admission. This should be balanced against the possibility of missing a patient with an SBI. In the derivation set, 0.2%, 95% CI (0, 1.1%) of the patients who met low risk criteria had an SBI. Procalcitonin would need to be available in a time frame that would influence decision making.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

APPENDIX: ACUTE ILLNESS (AKA YALE) OBSERVATION SCORE

ACUTE ILLNESS OBSERVATION SCORE (FEBRILE CHILDREN 3-36 MONTHS)	
QUALITY OF CRY	
Strong or no cry	1
Whimper or sob	3
Weak cry, moan, or high-pitched cry	5
REACTION TO PARENTS	
Brief cry or content	1
Cries off and on	3
Persistent cry	5
STATE VARIATION	
Awakens quickly	1
Difficult to awaken	3
No arousal or falls asleep	5
COLOR	
Pink (1 point)	1
Acrocyanosis	3
Pale, cyanotic, or mottled	5
HYDRATION	
Eyes, skin, and mucus membranes moist	1
Mouth slightly dry	3
Mucus membranes dry, eyes sunken	5
SOCIAL RESPONSE	
Alert or smiles	1
Alert or brief smile	3
No smile, anxious, or dull	5
Range (6-30), > 10 considered high risk for serious illness TOTAL	

McCarthy PL, Lembo RM, Fink HD, Baron MA, Cicchetti DV.
Observation, History, and Physical Examination in Diagnosis of Serious Illnesses in Febrile Children Less Than or Equal to 24 Months.
J Pediatr. 1987 Jan;110(1):26-30., PubMed ID: 3540248

FEBRILE NEONATE: PHILADELPHIA CRITERIA

In febrile neonates, between 29 and 56 days of age, do history, examination and laboratory parameters ("Philadelphia Criteria") accurately identify those at low risk for a serious bacterial infection who could be safely managed as outpatients without antibiotics?

Michael Mojica, M.D

May 30, 2017

Baker MD, Bell LM, Avner JR.

OUTPATIENT MANAGEMENT WITHOUT ANTIBIOTICS OF FEVER IN SELECTED INFANTS.

N Engl J Med. 1993 Nov 11;329(20):1437-41.
PubMed ID: 8413453

STUDY DEFINITIONS	
POPULATION	Inclusion: 29-56 days, presumed immunocompetent, rectal temperature ≥ 38.2 Exclusion: None specified Setting: Single Children's Hospital ED, 7/1987-6/1992
RULE PARAMETERS	Standardized History and Examination • Complete history obtained from parents • Physical examination completed by attending • Infant observation score (see Appendix) assigned by attending • In the 3rd study year "No recognized immunodeficiency syndrome" was added as a criterion based on preliminary data analysis Standardized Laboratory Evaluation • WBC < 15,000/mm^3 • Microscopic urinalysis (catheterized): < 10 WBC/hpf AND few or no bacteria • Chest XRAY (2 views): No distinct infiltrate confirmed by radiology attending • Lumbar puncture: < 8 WBC/hpf (non-bloody specimen) • Lumbar puncture: Negative gram stain • Bacterial cultures of blood, urine and CSF • Stool for WBC and stool culture if history of diarrhea • In the 3rd study year a "Band to Neutrophil ratio < 0.2" was added as a criterion based on preliminary data analysis A. Criteria Positive Patients: Admitted empiric antibiotics 1. Abnormal laboratory values as described above 2. Evidence of Infection on physical examination 3. Infant observation score > 10 4. Spinal fluid that was grossly bloody and therefore uninterpretable. B. Criteria Negative Patients: 1. Normal laboratory values as described above 2. No evidence of Infection on physical examination 3. Infant observation score ≤ 10 B1. Outpatient observation without antibiotics (Even days) Required to live within 30 minutes of the hospital, working phone at home, agree to a return visit on the next 2 days. B2. Inpatient observation without antibiotics (Odd days)
REFERENCE STANDARD	Serious Bacterial Infection: Bacterial growth of a known pathogen in cultures of blood, urine, CSF or stool, clinically apparent cellulitis or abscess Serious Illness: 1. Serious bacterial infection (see above), 2. Pneumonia, or 3. Aseptic meningitis Urine Culture: Negative if < 1000 CFU/ml of a single organism. Contaminated if ≥ 10^5 CFU with ≥ 3 colony types with none predominant Blood Culture: Contaminated if symptoms resolved without treatment (Coagulase negative staphylococcus) or non-pathogenic bacteria isolated. Pneumonia: Discrete infiltrate confirmed by attending radiologist Aseptic Meningitis: CSF pleocytosis (≥ 8 WBC/hpf in a non-bloody specimen), without a bacterial pathogen and no prior antibiotics.

DISPOSITION AND TREATMENT	A. <u>Criteria Positive Patients</u>: Admitted, empiric antibiotics administered 1. Abnormal laboratory values as described above 2. Evidence of infection on physical examination 3. Infant observation score > 10 4. Spinal fluid tgrossly bloody and therefore uninterpretable. B. <u>Criteria Negative Patients</u>: 1. Normal laboratory values as described above 2. No evidence of infection on physical examination 3. Infant observation score ≤ 10 B1. Outpatient observation without antibiotics (Even days) Required to live within 30 minutes of the hospital, have a Working phone at home, agree to a return visit on each of the next 2 days. B2. Inpatient observation without antibiotics (Odd days)
OUTCOME	Rule Characteristics
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. History, physical examination and laboratory predictors were included in the analysis. Details of the history elements obtained were not provided.
Were all important predictors present in significant proportion of the study population?	Unclear. Data on the prevalence of each predictor used were not provided.
Were the outcome event and predictors clearly defined?	Yes. Each of the predictors as well as the outcome of serious bacterial infection are cleared defined.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Yes. The outcome of serious bacterial infection was primarily defined by the presence of bacterial cultures. It is unclear if those reviewing the culture results were aware of the presence of the predictors though it is unlikely that knowledge of the predictors would influence the assessment of the outcome.
Was the sample size adequate (including an adequate number of outcome events)?	Unclear. In general, 10 outcomes are required for each variable included in a rule derived by logistic regression. The study included a total of 747 patients of which 65 (8.7%) had a serious bacterial infection.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

N = 747
Inpatient/Antibiotics: 460 (61.6%)
Outpatient/No antibiotics: 139 (18.6%)
(2 subsequently admitted, both without SBI)
Inpatient/No antibiotics: 148 (19.8%)
(2 received antibiotics, 1 bacteremia, 1 aseptic meningitis)

INFECTIONS

	INPATIENT ANTIBIOTICS	OUTPATIENT OBSERVATION	INPATIENT OBSERVATION
SBI	64	0	1
Pneumonia	28	0	0
Aseptic men	100	0	1
Otitis media	18	0	0
Viral*	250	139	146
Serious**	192	0	2

* Viral syndrome, gastroenteritis, or cystitis, varicella and bronchiolitis
** Serious = SBI or Pneumonia or Aseptic Meningitis

Unmodified Criteria*		SERIOUS BACTERIAL INFECTION		
		YES	NO	
SCREENING	POSITIVE	64	396	460
	NEGATIVE	1	286	287
		65	682	747

*Does not include: band/neutrophil ratio < 0.2 or no recognized immunodeficiency syndrome

Prevalence: 65/747 = 8.7%
Sensitivity: 64/65 = 98.5%, 95% CI (91.8, 99.7%)
Specificity: 286/682 = 41.9%, 95% CI (38.3, 45.7%)
Predictive Value (+): 64/460 = 13.9%, 95% CI (11, 17.4%)
Predictive Value (-): 286/287 = 99.7%, 95% CI (98.1, 99.9)
Likelihood Ratio (+): (64/65)/(396/682) = 1.7, 95% CI (1.6, 1.8)
Likelihood Ratio (-): (1/65)/(286/682) = 0.04, 95% CI (0.005, 0.026)

Sensitivity and predictive value of a negative rule increased to 100% when the band/neutrophil ratio and no recognizable immunodeficiency syndrome were later added to the criteria. This would likely decrease the specificity and predictive value of a positive rule but the updated rule characteristics were not reported and could not be calculated from the data provided.

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?
62.4% (287/460) of patients in the unmodified rule were considered as “screening negative. If the baseline rate of admission with antibiotics were 100% before implementation of the rule then admission for antibiotics could be reduced by 37.6% (100% - 62.4%).
WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?
No. There was no internal statistical validation of the rule.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied?	☐ I ☐ II ☐ III ? ■ IV This is a difficult rule to classify. At best, it would be considered a level IV rule. Level IV rules have been derived only or validated only in split samples, large retrospective databases or by statistical methods. Level IV rules require further validation before they can be applied clinically. However, this rule was not statistically derived. The rule was instead assembled from potential predictors with predefined cutoffs. It may be unfair to apply the rule classification scheme to a study that pre-dated clear methodologic standards for clinical decision rules.
Does the rule make clinical sense?	Yes. Those with physical exam findings consistent with a bacterial infection and those with a positive urinalysis, positive CSF findings or those with elevated biomarkers would be expected to have a higher risk of serious bacterial infection.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. The laboratory parameters should be reproducible. There was however, no measure of inter-rater reliability for the physical examination findings or for the acute illness observation score.
Is the rule applicable to the patients in my practice?	Likely Yes. The study population was from a single institution and demographic characteristics provided are limited to the age and gender of the patients. However, the rate of serious bacterial infection in the study population is like that typically presented in the literature.
Will the rule results change my management strategy?	Yes. The criteria provide a structure to the evaluation of the febrile neonate. This study demonstrated that outpatient management of febrile neonates without empiric antibiotics is feasible.
What are the benefits of applying the rule to my patients?	The potential benefits of applying the criteria is a reduction in admission and a reduction in antibiotic administration for those at low risk of serious bacterial infection. This could reduce inpatient complications such as nosocomial infection and reduce antibiotic related adverse events and possibly reduce antibiotic resistance.
What are the risks of applying the rule to my patients?	The primary risk is in sending home and not treating with antibiotics a patient with a serious bacterial infection. In this study 1 patient considered at low risk for serious bacterial infection had a serious bacterial infection. With the addition of the band to neutrophil ratio 0 patients with serious bacterial infection were missed. The lower limits for the confidence intervals for sensitivity (91.8%) and the predictive value of a negative rule (98.1%) indicate that there is a possibility of missing patients with serious bacterial infection.

CLINICAL BOTTOM LINE

BACKGROUND: At the time this study was published the standard practice was to complete a full sepsis evaluation and admit all febrile neonates less than 2-3 months of age for antibiotics pending culture results. Approximately 90% of infants who were admitted did not have a serious bacterial infection. Those admitted were at risk for nosocomial infections, complication such as intravenous catheter infiltration and antibiotic related adverse events. If a cohort of infants at very low risk of serious bacterial infection could be identified based on history, examination and laboratory findings available in a timely fashion then they could potentially benefit from fewer admissions and antibiotic treatment.

CLINICAL QUESTION: In febrile neonates, between 29 and 56 days of age, do history, examination and laboratory parameters (the “Philadelphia Criteria”) accurately identify those at low risk for a serious bacterial infection who could be managed as outpatients without antibiotics?

DESIGN/RISK OF BIAS: The authors sought to evaluate criteria that would be available at the time of clinical decision making to identify patients at low risk for serious bacterial infection that could be managed as outpatients without empiric antibiotics. This was a prospective cohort of 747 neonates admitted of which 8.7% of patients had a serious bacterial infection. Urinary tract infection accounted for 33% of the serious bacterial infections (bacteremia 26%, bacterial gastroenteritis 18%, bacterial meningitis 13% and cellulitis 8%). Patients not meeting risk criteria were admitted for intravenous antibiotics. Those meeting low risk criteria were selected based on odd or even numbered days to 1. admission without intravenous antibiotics or 2. discharge without intravenous antibiotics with close follow up.

This was not a derivation of a clinical decision rule in that a regression analysis was not used to identify independent predictors of serious bacterial infection. Potential predictors were chosen based on clinical experience and the existing literature.

PRIMARY RESULTS: The rule parameters correctly identified the majority of patients with a serious bacterial infection (Sensitivity 98.5%, 95%CI (91.8, 99.7%), Predictive Value of a Negative Rule 99.7%, 95% CI (98.1, 99.9). The rule parameters did not perform as well identifying those without a serious infection (Specificity 41.9%, 95% CI (38.3, 45.7%), Predictive Value of a positive rule of 13.9%, 95% CI (11, 17.4%). The rule essentially divided a population with an 8.7% risk of serious bacterial infection into a low risk group with a 0.3% risk of serious bacterial infection (1 - Predictive Value of a Negative Rule 99.7%, 95% CI (98.1, 99.9)) and a high-risk group with a 13.9% risk of serious bacterial infection. (Predictive Value of a Positive Rule = 13.9%, 95% CI (11, 17.4%).

Sensitivity and predictive value of a negative rule increased to 100% when the band/neutrophil ratio and no recognizable immunodeficiency syndrome were later added to the criteria. This would likely decrease the specificity and predictive value of a positive rule but the updated test characteristics were not reported and could not be calculated from the data provided.

62.4% (287/460) met criteria for low risk of serious bacterial infection. Theoretically, these patients could not be managed as outpatients without antibiotics if the caregivers are reliable, accessible by phone and agree to follow up. If the baseline rate of admission with antibiotics were 100% before implementation of the rule then admission for antibiotics could be reduced by 37.6% (100% - 62.4%).

APPLICABILITY: The study population was from a single institution and demographic characteristics provided are limited to the age and gender of the patients. Though the majority of the criteria were objective laboratory measure the Inter-rater reliability for physical examination findings and the acute illness observation score were not presented. However, the rate of serious bacterial infection in the study population is similar to that typically presented in the literature.

This is a difficult rule to classify. At best, it would be considered a level IV rule. Level IV rules have been derived only or validated only in split samples, large retrospective databases or by statistical methods. Level IV rules require further validation before they can be applied clinically. However, this rule was not statistically derived. The rule was instead assembled from potential predictors with predefined cutoffs. It may be unfair to apply the rule classification scheme to a study that pre-dated clear methodologic standards for clinical decision rules.

AUTHOR'S CONCLUSION: "We conclude that it is possible to identify a group of febrile infants more than 28 days of age who are at low risk for serious bacterial illness and who can be safely and effectively cared for at home without antibiotics. We caution those who chose to treat infants in this way that they must first evaluate the infants carefully and completely and that subsequent evaluation procedures must be strictly carried out. Meticulous adherence to this management strategy should prove both safe and cost effective."

POTENTIAL IMPACT: The Philadelphia criteria provide a structured approach to the evaluation of the febrile neonate. The authors emphasize that both the examination and laboratory criteria are essential as some patients with serious bacterial infections only had abnormalities in only one category of these.

This study demonstrated that outpatient management of febrile neonates without empiric antibiotics is feasible. The potential benefits of applying the Philadelphia Criteria is a reduction in admission and a reduction in antibiotic administration for those at low risk of serious bacterial infection. This could reduce inpatient complications such as nosocomial infection and reduce antibiotic related adverse events and possibly reduce antibiotic resistance.

APPENDIX: PHILADELPHIA CRITERIA (1993)

PHILADELPHIA CRITERIA: LOW RISK FOR SERIOUS BACTERIAL INFECTION
HISTORY AND EXAMINATION
Age 29-56 days
No recognized immunodeficiency syndrome
Well appearing
Physical examination without localizing signs of a bacterial infection
Infant observation score < 10 (See Appendix)
SOCIAL
Lives within 30 minutes of the hospital
Working home phone
Agree to a return visit on each of the next 2 days
LABORATORY EVALUATION
WBC < 15,000/mm^3
Band to Neutrophil ratio < 0.2 (Bands/(Bands + Neutrophils)
Urinalysis (catheterized specimen): < 10 WBC/hpf AND few or no bacteria
Chest XRAY without evidence of a distinct infiltrate
CSF WBC < 8 WBC/hpf (in a non-bloody specimen)
CSF negative gram stain
Stool for WBC (if history of diarrhea): No RBC, Few or No WBC

WEB LINK: UPDATED PHILADELPHIA CRITERIA

APPENDIX: CLINICAL DECISION RULES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

APPENDIX: ACUTE ILLNESS OBSERVATION SCORE

ACUTE ILLNESS OBSERVATION SCORE (FEBRILE CHILDREN 3-36 MONTHS)	
QUALITY OF CRY	
Strong or no cry	1
Whimper or sob	3
Weak cry, moan, or high pitched cry	5
REACTION TO PARENTS	
Brief cry or content	1
Cries off and on	3
Persistent cry	5
STATE VARIATION	
Awakens quickly	1
Difficult to awaken	3
No arousal or falls asleep	5
COLOR	
Pink (1 point)	1
Acrocyanosis	3
Pale, cyanotic, or mottled	5
HYDRATION	
Eyes, skin, and mucus membranes moist	1
Mouth slightly dry	3
Mucus membranes dry, eyes sunken	5
SOCIAL RESPONSE	
Alert or smiles	1
Alert or brief smile	3
No smile, anxious, or dull	5
TOTAL SCORE	
Score > 10 is considered high risk for serious illness	

McCarthy PL, Lembo RM, Fink HD, Baron MA, Cicchetti DV.
Observation, History, and Physical Examination in Diagnosis of Serious Illnesses in Febrile Children Less Than or Equal to 24 Months.
J Pediatr. 1987 Jan;110(1):26-30., PubMed ID: 3540248

FEBRILE NEONATE:
PRIVATE PRACTICE MANAGEMENT

In the infant less than 3 months of age with fever ≥ 38°C
in the private practice setting…

Q1. What is the epidemiology of serious bacterial infection?
Q2. How well do private practitioners adhere to published guidelines?
Q3. How accurately do private practitioners identify those with bacteremia and/or bacterial meningitis?
Q4. Can clinical predictors identify infants at low risk for bacteremia and/or bacterial meningitis?

Karen Franco M.D., James Tsung, M.D.
July 2004

Pantell RH, Newman TB, Bernzweig J, Bergman DA, Takayama JI, Segal M, Finch SA, Wasserman RC.

MANAGEMENT AND OUTCOMES OF CARE OF FEVER IN EARLY INFANCY

JAMA. 2004 Mar 10;291(10):1203-12.
PubMed ID: 15010441

STUDY DEFINITIONS	
POPULATION	Inclusion: ≤ 3 months, discharged from hospital as a newborn, temperature ≥ 38°C at home or in clinician's office, no other major comorbidities (e.g. congenital anomalies, extreme prematurity, conditions associated with organ system failure). Exclusion: None described Setting: The pediatric research in office settings (PROS) network. 219 practices throughout the U.S. submitted data, 2/1995-4/1998
INTERVENTION	Standardized data collection sheet Clinical appearance defined as: well, minimally well, moderately ill, very ill Laboratory testing performed at the discretion of the clinician
CONTROL	Bacteremia, bacterial meningitis (urinary tract infection excluded)
OUTCOME	Q1. Prevalence of bacteremia and bacterial meningitis. Q2; Adherence to published guidelines Q3. Sensitivity of identifying bacteremia and/or bacterial meningitis. Defined as initiating antibiotics prior to culture results. Q4. Rule characteristics
DESIGN	Observational: Prospective cohort Q1-3: Case series Q4: Derivation of a clinical decision rule

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Unclear. Fever, age and clinical appearance (very ill, moderately ill, well, inattentive, no smile, decreased social interaction) were the only predictors identified.
Were all important predictors present in significant proportion of the study population?	Unclear. The percentage of patients with each predictor was not presented. It may not be possible to evaluate the contribution of predictors that did occurred rarely.
Were the outcome event and predictors clearly defined?	The predictor fever was clearly defined at > 38°C in an infant < 3 months of age. However, clinical appearance (very ill, moderately ill, well appearing) was not clearly defined. Outcomes defined as bacteremia (positive blood culture) and meningitis (positive CSF profile or CSF culture). However, not all infants in the study had Blood and CSF cultures performed. The evaluation and management of these patients was at the MD's discretion. Some patients who received antibiotics for another indication did not have cultures sent. This could potentially mask some outcomes of interest.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Enrolling physicians assessing presence of predictors did not know the outcomes until laboratory testing results were available. Bias was unlikely given that outcomes were dependent on objective laboratory evidence (e.g., culture positive or negative). To minimize bias or misclassification, cases were reviewed by an infectious disease consultant and an external reviewer.
Was the sample size adequate (including an adequate number of outcome events)?	Despite a large initial cohort this study represented a rule derived on only 63 cases of bacteremia and/or meningitis. Confidence intervals were not presented

WHAT ARE THE RESULTS?

Q1. EPIDEMIOLOGY?

N = 3,066
70% white, non-Hispanic
73% well or minimally ill
Bacteremia: 2.4% (those blood culture sent), 1.8% overall
Bacterial meningitis: 0.5% (5 patients with both)
E coli #1 account for 30% of bacteremia, 15% of meningitis UTI: 5.4% (10.7% of which had bacteremia)
Otitis media: 12.2%

Q2: ADHERENCE TO PUBLISHED GUIDELINES?

AGE	APPEARANCE	GUIDELINE RECOMMENDATION	ADHERENCE
< 31 days	All	Full sepsis evaluation, antibiotics, admit	45.7%
31-90 day	Moderately ill-Very ill	Full sepsis evaluation, antibiotics, admit	35.8%
31-90 day	Normal-Mildly ill	WBC, UA	41.6%

50% no urine obtained, 25% without blood or CSF obtained
54% with more than 1 follow-up visit and 68% with 1 or more phone calls

Q3: IDENTIFICATION OF THOSE WITH BACTEREMIA/ BACTERIAL MENINGITIS?

Note: The definition of specificity in this study was non-standard
Numerator: children not treated initially with antibiotics
Denominator: infants without bacteremia/bacterial meningitis and other conditions requiring antibiotics (i.e. otitis media, urinary tract infection, pneumonia),

Sensitivity: 97.1% (64/66) Identified (treated with antibiotics)
Specificity: 35.5%

Q4: RULE CHARACTERISTICS

Recursive partitioning created a model the included 3 variables.
Patients were considered low risk if:
1. Appearance of “Well” or “minimally ill” appearing
2. Age ≥ 25 days
3. T < 38.6 C

Sensitivity: 93.8%.
Specificity: 27.3%.
Negative predictive value: 99.6% (0.4% of patients with a negative rule will have bacteremia or bacterial meningitis)

The rule classified 34% of patients as low risk. The reduction in resource utilization with depend on the current baseline rate of resource utilization. There was no internal statistical validation of the rule

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied?	☐ I ☐ II ☐ III ■ IV (See appendix) Level IV rules have been derived only or validated only in split samples, large retrospective databases or by statistical methods. A level IV rule requires further validation before it can be applied clinically.
Does the rule make clinical sense?	Yes. Younger patients with a higher temperature, younger age and have a sicker appearance were more likely to have a serious bacterial infection.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	The rule may not be reproducible. The interpretation of individual predictors is somewhat subjective. In particular, the clinical appearance of the patient was poorly defined (well, minimally ill or moderate/severely ill). Intra-observer reliability of predictors was not assessed
Is the rule applicable to the patients in my practice?	This is a level 4 clinical prediction and should not be applied until validated. In addition, the experience with private practice patients may not be generalizable to other settings such as hospital based clinics or emergency departments. It appears that one of the keys to accurate diagnosis is close and frequent follow-up which may not be feasible in other settings. The rates of bacteremia (1.8%) and meningitis (0.5%) were comparable to published ED studies. The large geographic area of the U.S included should make the results generalizable to the private practice setting. The low rate of Streptococcus pneumoniae makes the results applicable to post to Prevnar epidemiology
Will the rule results change my management strategy?	This would depend on the current management strategy. The patients in this study had lower rates of interventions including: diagnostic testing, antibiotics and admission than that prescribed by existing guidelines
What are the benefits of applying the rule to my patients?	The primary benefit of applying the rule is a reduction in ancillary testing and hospital admission. Both of these have been associated with their own complications.
What are the risks of applying the rule to my patients?	The primary risk is in missing cases of bacteremia or meningitis was potential for serious sequelae. The rule would have misclassified 6.3% of patients with bacteremia/meningitis as low risk or 1 in 1000 patients

CLINICAL BOTTOM LINE

BACKGROUND: Febrile infants have an approximately 10% risk of a serious bacterial infections. The majority of these infections are urinary tract infections but a few percent will have bacteremia and/or meningitis. The epidemiology of these infections has evolved over time due to new vaccines. These infections cannot be diagnosed solely based on physical examination finding. The extent of laboratory testing and the need for admission and antibiotics pending culture results are a matter of great debate. A number of clinical decision instruments such as the Rochester, Philadelphia and Boston criteria have been developed to identify the febrile neonate at low risk for serious bacterial infection. The majority of the literature on this topic is based on emergency department patients. How these patients are approached in a private practice setting has not been extensively reported.

CLINICAL QUESTION: In the infant < 3 months of age with a fever ≥ 38°C in the private practice setting…
Q1. What is the epidemiology of serious bacterial infection?
Q2. How well do private practitioners adhere to published guidelines?
Q3. How accurately do private practitioners identify those with bacteremia or bacterial meningitis?
Q4. Can clinical predictors identify infants with bacteremia, bacterial meningitis?

DESIGN/RISK OF BIAS: This was a well-designed study in the outpatient setting of the PROS network (Pediatric Research in the Office Setting) that included 3,066 predominantly white patients who had a clinical appearance of normal or mildly ill.

PRIMARY RESULTS:
Q1: The rate of bacteremia was 2.4% of those with blood culture sent and 1.8% overall. Bacterial meningitis occurred in 0.5% with 1/3 also having bacteremia. E coli was the predominant organism accounting for 30% of bacteremia and 15% of meningitis. Half of the case of bacteremia and meningitis occurred in patients < 1 month of age. A urinary tract infection (5.4%) was the most common cause of serious bacterial infection (10.7% of which also had bacteremia). The spectrum of illness is consistent with what has been seen in ED based studies.

Q2: The management of febrile infants less than 3 months in the outpatient setting does not adhere to published guidelines. Office Pediatricians followed published guidelines an average of 42% of the time. Office pediatricians manage febrile infants more "liberally" with less testing, antibiotics and admissions and with close follow-up. The degree of follow-up may not be feasible in the ED setting.

Q3: The study practitioners identified 61of 63 (96.8%) cases of bacteremia/meningitis with empiric antibiotics. This should be interpreted in the context that 12.2% were diagnosed with acute otitis media and treated with antibiotics. This is an incredibly high prevalence of acute otitis media in this population and may account for the high sensitivity in the study (defined as treating patients with bacteremia or meningitis). The percentage of those with bacteremia and/or bacterial meningitis who were initially treated for acute otitis media was not reported. Whether oral or parenteral antibiotics were used and whether patients treated for otitis media had blood cultures sent was also not reported. There were 2 patients with bacteremia or meningitis that were not identified. Both patients were subsequently treated without complications.

Q4: A clinical prediction model using binary recursive partitioning was developed to identify infants at low risk for bacteremia/bacterial meningitis. Only clinical parameters were included. Patients were considered low risk if: they appeared well or minimally ill, were ≥ 25 days of age and had a temperature of < 38.6 C. The rule sensitivity was 93.8% and specificity was. 27.3%. The negative predictive value was 99.6% indicating 0.4% of patients with a negative rule will have bacteremia or bacterial meningitis. This is a stage IV decision rule and requires further validation before it can be applied clinically.

APPLICABILITY: This is a level 4 clinical prediction rule and should not be applied to patients unless validated. The subjectivity of clinical assessment and the small number of cases of bacteremia meningitis may limit the applicability of this data.

AUTHOR'S CONCLUSION: "In summary, we have documented strategies for managing fever in infants by community practitioners and the frequency of illnesses diagnosed. The large sample size has allowed us to precisely assess the frequency and factors associated with high risk of bacteremia/bacterial meningitis in infants (age ≤ 30 days, higher temperatures, ill appearance, abnormal cry, and abnormal WBC count); and we have identified a group with a risk of bacteremia/ bacterial meningitis of 0.4% (well appearing, aged 25 days or older, and temperature < 38.6°C). Despite lack of adherence to guidelines, PROS clinicians detected as many cases of bacteremia/bacterial meningitis while performing fewer tests and hospitalizing fewer infants than would have occurred if strictly adhering to practice parameters. The findings suggest that if close follow-up care is attainable, the management of selected cases by experienced clinicians using clinical judgment may be more appropriate than strict adherence to published recommendations, with the potential benefit of reducing considerable costs and iatrogenic morbidity. While guidelines have an important role in ensuring the quality of care for many clinical issues, their performance in complex clinical situations, such as the management of febrile illnesses, should be analyzed to evaluate whether the guidelines actually optimize care."

POTENTIAL IMPACT: The study indicates that the rate of serious bacterial infection in the private practice setting is similar to that found in ED based studies. Private practitioners seldom followed published guidelines for laboratory investigation, antibiotics or admission. The private practitioners treated 96.9% of those subsequently identified with bacteremia or bacterial meningitis. However, it is unclear if this sensitivity occurred due to treating a very high percentage (12.2%) with antibiotics for acute otitis media. The derived decision rule using only clinical parameters requires further validation.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

FEBRILE NEONATE: PROCALCITONIN

In febrile neonates 7-91 days of age what is the diagnostic accuracy of Procalcitonin (PCT) in identifying serious bacterial infections (SBI) and invasive bacterial infections (IBI) both independently and in comparison to other biomarkers?

Shweta Iyer M.D., Michael Mojica M.D.
October 2016

Milcent K, Faesch S, Gras-Le Guen C, Dubos F, Poulalhon C, Badier I, Marc E, Laguille C, de Pontual L, Mosca A, Nissack G, Biscardi S, Le Hors H, Louillet F, Dumitrescu AM, Babe P, Vauloup-Fellous C, Bouyer J, Gajdos V.

USE OF PROCALCITONIN ASSAYS TO PREDICT SERIOUS BACTERIAL INFECTION IN YOUNG FEBRILE INFANTS.

JAMA Pediatr. 2016 Jan;170(1):62-9.
PubMed ID: 27088558

STUDY DEFINITIONS	
POPULATION	Inclusion: 7-91 days, temperatures ≥ 38°C at home or on admission Exclusion: Comorbidities: immune deficiency, congenital abnormality, or chronic disease. Antibiotic treatment within 48 hours. Infants ≤ 6 days not included (more likely to have early-onset sepsis related to perinatal factors and PCT levels during the first 3 days of life are higher) Setting: Multicenter Pediatric EDs (15 in France), 10/08-3/11
TEST	Procalcitonin Comparison: WBC, ANC and CRP
REFERENCE STANDARD	Definite SBI: Pathogen (+) blood culture, CSF culture, stool culture, urine culture Definite IBI: Pathogen (+) blood culture, CSF culture
OUTCOMES	1. Procalcitonin area under the receiver operating characteristic curve (AUC) as a measure of diagnostic accuracy) for both SBI and IBI 2. Determination of optimal Procalcitonin cut-off, likelihood ratios for that cutoff 3. Comparison: AUC for Procalcitonin, WBC, ANC and CRP for both SBI and IBI 4. Regression analysis: Independent predictors of SBI and IBI
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients present a diagnostic dilemma?	Yes. It is often difficult to distinguish infants at risk of IBI/SBI vs. infants with a viral illness, and to determine the extent of workup. Management of such cases could be improved by new biomarkers, such as Procalcitonin (PCT)
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The independent reference standard was the diagnosis of SBI/IBI by blood, CSF, stool, or urine cultures for SBI, and blood and CSF cultures for IBI.
Were those interpreting the test and reference standard blind to the other results?	Yes. The attending physician made the diagnosis, categorized as SBI or no bacterial infection, masked to the PCT value. All cases of IBI were reviewed by 2 pediatric infectious disease specialists and 2 bacteriologists that were masked to the PCT results. The laboratory was not informed of the clinical features while doing the PCT analysis.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	No. There was no standardized evaluation in the study and not all patients received the reference standards for SBI and IBI. 61% of patients had a blood culture, and 65% of patients had a lumbar puncture. In addition, all negative urinalysis did not have a urine culture sent.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 2,047 (7-30 days = 415, 31-91 days = 1,632)
SBI = 139/2,047 = 6.8% (11% of those with BCx sent)
UTI: 115/139 = 83% of SBI)
IBI = 21/2,047 = 1% (0.6% bacteremia, 0.4% meningitis)

AREA UNDER THE ROC CURVE

	Serious Bacterial Infection	Invasive Bacterial Infection
PCT	0.81 (0.75, 0.86)	0.91(0.83, 0.99)
CRP	0.80 (0.75, 0.85)	0.77 (0.65, 0.89)*
ANC	0.73 (0.66, 0.79)*	0.61 (0.45, 0.77)*
WBC	0.66 (0.58, 0.73)*	0.48 (0.31, 0.66)*
*Statistically significant difference from PCT		

PROCALCITONIN AT A CUTOFF OF ≥ 0.3 NG/ML

	Sensitivity	Specificity	Likelihood Ratio (+) Test	Likelihood Ratio (-) Test
SBI	74%	78%	3.3	0.3
IBI	90%	78%	4.0	0.1

LOGISTIC REGRESSION: PREDICTORS

	ADJUST ODDS RATIO SERIOUS BACTERIAL INFECTION	ADJUSTED ODDS RATIO INVASIVE BACTERIAL INFECTION
PCT ≥ 0.3	4.5 (2.3-8.8)	40.3 (5.0-332)
CRP ≥ 20	4.2 (2.1-8.4)	NS

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	Yes. The test is objective and reproducible. Unclear if we use the same PCT assay though the reproducibility should be similar in our clinical setting.
Are the study results applicable to the patients in my practice?	The study population is febrile infants 7-91 days old, without antibiotic treatment or comorbidities. It is difficult to compare the discharged patients to our population of discharged patients, since in the study the discharged patients were followed up after 48 hours with a medical visit or telephone call, and ED patients are often lost to follow-up. In addition, there is a higher percentage of moderately or very ill patients in their study (31%) as compared to our typical percentage of ill appearing patients in the ED. However, the rates of SBI and IBI of the population in the article are similar to the rates of these infections in ED literature.
Will the results change my management strategy?	Not necessarily. All patients, including the moderate to severely ill patients, received a PCT. I probably would go straight to treating these ill patients in addition to doing diagnostic studies (i.e. cultures, CXR). Additionally, if a patient had a source for infection i.e. positive UA (many of the patients had E. Coli as a source of infection), I would not get a PCT if the clinical picture fits the source and can be appropriately treated.
Will patients be better off as a result of the test?	The PCT seems to be most useful in patients who are at low to moderate risk of SBI, since it may change the management of these patients. A small likelihood ratio of a negative test for IBI indicates a low risk of IBI. The assay may help identify IBI earlier, but as stated above, diagnostic and therapeutic management is likely to be started early regardless of PCT value in patients who have a clinical picture consistent with IBI.

CLINICAL BOTTOM LINE

BACKGROUND: Severe bacterial infections (SBIs), including UTI, bacterial gastroenteritis, and invasive bacterial infections (IBIs), including bacteremia and meningitis, have a prevalence of 5-15% in infants younger than 3 months, with few reliable symptoms or clinical findings to aid in identifying those at highest risk. Management of these cases could be improved by adding diagnostic tests to clinical assessment. PCT assays have been shown in some studies to have better diagnostic accuracy than other biomarkers (i.e. CRP, WBC, ANC).

CLINICAL QUESTION: In febrile neonates 7-91 days of age what is the diagnostic accuracy of Procalcitonin (PCT) in identifying serious bacterial infections (SBI) and invasive bacterial infections (IBI) both independently and in comparison to other biomarkers?

DESIGN/VALIDITY: This was a prospective, multicenter, cohort study in 15 French pediatric emergency departments. 2,047 infants from 7-91 days with a fever of 38°C or higher at home were enrolled. Those with comorbidities and/or antibiotic treatment within the previous 48 hours were excluded. However, not all patients had all reference standards obtained for SBI/IBI (ie. Blood, CSF, stool, urine for SBI, blood/CSF for IBI). In addition, no data showing how many patients received a UA alone without a urine culture, or what defined a patient looking moderately or very ill clinically were presented.

PRIMARY RESULTS: The AUC for Procalcitonin for the identification of invasive bacterial infection (AUC, 0.91; 95% CI, 0.83-0.99) was significantly higher than that of the CRP (AUC, 0.77; 95% CI, 0.65-0.89; *P* = .002). At a cutoff value of ≥ 0.3 ng/mL for identifying invasive bacterial infection, PCT had a negative likelihood ratio of 0.1 (0.03-0.4) and a positive likelihood hood ratio of 4.0 (3.3-4.8). In the logistic regression analysis, Procalcitonin was the only independent predictor of invasive bacterial infection (adjusted OR 40.3 (5.0-332)). However, urinalysis and clinical status were not included in the regression analysis. 25% (2/8) of the meningitis and 62% (8/13) of the bacteremia was caused by E Coli, presumably from a urinary tract infection. If the urinalysis was positive in these patients or the clinical status was moderately to severely ill, then Procalcitonin would be of less diagnostic utility.

Procalcitonin performance for the identification of serious bacterial infection was similar to that of CRP. Overall, the PCT has better test characteristics than CRP for identifying invasive bacterial infection. PCT has similar diagnostic properties as CRP measurement for detecting definite serious bacterial infection. Procalcitonin was more accurate in predicting both invasive bacterial infection and serious bacterial infection when compared to WBC and ANC.

APPLICABILITY: The study population is likely generalizable to our patient population who do not meet exclusion criteria. The rates of SBI and IBI of the population in the article are similar to the rates of these infections in the literature from U.S. pediatric emergency departments. However, there was a higher percentage of patients described as moderately or very ill patients in the study (31%). The parameters for determining the clinical impression of moderately or very ill patients is not described. Clinical decision making in ill-appearing patients is simplified with patients undergoing a full laboratory assessment and antibiotic therapy. Procalcitonin is unlikely to influence clinical decision making in ill-appearing patients or those with a urinalysis suggestive of a urinary tract infection/

AUTHORS CONCLUSIONS: “Our large prospective study reveals that PCT is the best marker for identifying bacteremia and bacterial meningitis in febrile infants 7 to 91 days old and that it is moderately useful for identifying infants with SBIs. However, urinalyses are reliable to detect SBI, mainly represented by UTI in this age group, contrary to IBI. The performance of PCT testing should encourage the development of decision-making rules that incorporate PCT. Their effectiveness, cost, and the associated iatrogenic morbidity should be analyzed; these approaches should then be validated to determine how they should be combined to improve the management of febrile infants 7 to 91 days old.”

POTENTIAL IMPACT: Procalcitonin may be most useful in patients who are at low to moderate risk of SBI, since it may change the management of these patients. This assay could potentially allow us to avoid more invasive studies such as a lumbar puncture in patients with a low likelihood of bacterial infection. The assay may help identify invasive bacterial infections earlier, but diagnostic and therapeutic management is likely to be started early regardless of PCT value in patients who have a clinical picture consistent with invasive bacterial infection. Additionally, if a source of infection is clear i.e. positive UA, a PCT is unlikely to change management. The risks and benefits of PCT assay need to be weighed in each patient encounter. Ultimately, it is unlikely that any single test result or clinical variable will allow us to accurately distinguish the febrile infant with a serious or invasive bacterial infection from most infants with a viral process.

FEBRILE NEONATE:
RESPIRATORY SYNCYTIAL VIRUS

Do infants ≤ 60 days of age with a fever ≥ 38°C rectally who test positive for RSV when compared to infants who are RSV negative, have a decreased risk of serious bacterial infection?

Alexis Pankow, M.D., Martin Pusic, M.D., PhD.
September 2015

Levine DA, Platt SL, Dayan PS, Macias CG, Zorc JJ, Krief W, Schor J, Bank D, Fefferman N, Shaw KN, Kuppermann N; Multicenter RSV-SBI Study Group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics.

RISK OF SERIOUS BACTERIAL INFECTION IN YOUNG FEBRILE INFANTS WITH RESPIRATORY SYNCYTIAL VIRUS INFECTIONS

Pediatrics. 2004 Jun;113(6):1728-34.
PubMed ID: 15173498

STUDY DEFINITIONS	
POPULATION	Inclusion: Infants ≤ 60 days, fever ≥ 38°C rectally by history or ED evaluation, RSV test and any bacterial culture performed. Exclusion: Antibiotics within 48 hours of presentation, parental refusal, RSV testing or bacterial cultures were not obtained. Setting: 8 Pediatric ED. Seasonal: October-March 1998-2001
INTERVENTION	Clinical evaluation of RSV positive patients including: History Physical examination Bacterial cultures (Blood, CSF, Urine, and/or chest XRAY and stool). Follow up calls performed for patients discharged from ED 4-7 days after discharge
CONTROL	Patients without RSV
OUTCOME	Prevalence and relative risk of serious bacterial infection
DESIGN	Observational: Prospective, Cross sectional study

ARE THE RESULTS VALID?	
Was the sample of patients representative?	Probably. All patients were less than 60 days old with fever > 38C and all presumably had the same risk of the of serious bacterial infection defined as bacterial meningitis, bacteremia, UTI or bacterial enteritis. No information was reported regarding contacts with RSV or similar symptoms or daycare attendance where exposure rates would be much higher, if the children were premature or had received Synagis (if these children were excluded) or previous RSV infection. This information was reported as gathered but not included in the paper.
Were the patients sufficiently homogeneous with respect to prognostic risk?	Yes. (See Table 1). The groups were similar with regard to age, WBC, and ANC. RSV positive patients were 29% more likely to have upper respiratory symptoms and 31% more likley to have bronchiolitis.
Was follow-up sufficiently complete?	Patients with negative cultures who were discharged, were contacted 4-7 days after their visit. This was sufficient to determine if the child had meningitis because the child's illness would have progressed if they had bacterial meningitis
Were outcome criteria objective and unbiased?	Yes. All patients were tested for RSV with enzyme immunoassay or indirect florescent antibody from nasopharyngeal aspirates. Blood cultures, urine cultures and CSF cultures were sent on most patients. Patients without SBI who were missing a portion of the testing were excluded from analysis. The missed patients were later reported as having a higher rate of RSV. Perhaps those with RSV preferentially didn't have further testing (i.e. selection bias). Patients without CSF cultures but clinically well at follow up and had not received antibiotics were included and defined as not having bacterial meningitis.

WHAT ARE THE RESULTS?

HOW LIKELY ARE THE OUTCOMES OVER TIME?

		SERIOUS BACTERIAL INFECTION		
		YES	NO	
RSV	POSITIVE	17	227	244
	NEGATIVE	116	809	925
		133	1,036	1,169

Prevalence SBI: 133/1,169 = 11.4%
Prevalence SBI RSV Positive: 17/244 = 7%
Prevalence SBI RSV Negative: 116/925 = 12.5%

Relative Risk SBI (RSV(+)/(RSV(-))
= (17/244) /(116/925)
= 7%/12.5% = 0.55 95% CI (0.3-0.9)

Risk Difference SBI = AR(RSV(+) - AR(RSV(-)
= 7- 12.5%
= 5.5% 95%CI (0.012-0.09%)
(There is a 5.5% lower risk of SBI in patients who test positive for RSV than those who test negative for RSV)

SERIOUS BACTERIAL INFECTIONS

	RSV POSITIVE	RSV NEGATIVE	RELATIVE RISK 95%CI
UTI	5.4% (3.0-8.8%)	10.1% (8.3-12.2%)	0.6 (0.3-0.9%)
Bacteremia	1.1% (0.2-3.2%	2.3% (1.4-3.4%)	0.5 (0.1-0.6%)
Meningitis	0% (0.0-1.2%)	0.9% (0.4-1.7%)	0

HOW PRECISE ARE THE ESTIMATES OF LIKELIHOOD?

The confidence intervals surrounding the relative risk for the overall SBI, UTI, bacteremia and meningitis are not wide. This indicates that these relative risk values are fairly precise.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients and their management similar to those in my practice?	Yes. Some of the patients in the study were the patients at NYU/ Bellevue. The inclusion of 8 pediatric emergency departments improves the generalizability of the study results though the applicability to other clinical settings in unknown.
Was the follow up sufficiently long?	Yes. Follow up for non-admitted patients was 4-7 days. This follow up seems sufficient. Cultures are also monitored for a similar period of time for growth.
Can I use the results in the management of patients in my practice?	Yes. There is a 5.5% reduction in risk of SBI in the RSV positive group as compared to the RSV negative group. The overall prevalence of SBI in RSV positive patients was 7% so despite the reduction in risk it remains a significant risk that warrant continued testing for bacterial sources of infection in these infants. Number Needed to Harm 1/ARD = 1/0.055 = 18. An SBI evaluation of 18 RSV positive patients would identify one additional patient with an SBI. This may seem like a large number of negative work ups, but given the risk of a missed SBI, continued work ups are warranted. For meningitis, the NNH is approximately 100. A meningitis evaluation of 100 RSV positive patients would identify I one additional patient with meningitis.

CLINICAL BOTTOM LINE

BACKGROUND: In infants, less than 60 days old who present with fever there is often a question of what is the extent of the work-up necessary to identify serious bacterial infection. In those infants with evidence of a viral infection is their risk of serious bacterial infection low enough to preclude a serious bacterial infection evaluation?

CLINICAL QUESTION: Do infants ≤ 60 days old with a fever ≥ 38˚C rectally who test positive for respiratory syncytial virus (RSV) have a decreased risk of serious bacterial infection as compared to infants who are RSV negative?

DESIGN/VALIDITY: This is a well-designed, multicenter study including 1,169 febrile infants less than two months of age. The primary limitation of the study design is that it did not have sufficient power to conclusively determine the difference in rates of rare outcomes such as bacteremia and meningitis. In addition, patients who failed protocol and were not included in the study had a higher prevalence of RSV. If these patients were included the rate of serious bacterial infection may have been significantly less.

PRIMARY RESULTS: Infants who were RSV positive did have a lower risk of SBI 7% compared to 12.5% in RSV negative infants (RR = 0.55 95%CI 0.3-0.9). UTI was the most common serious bacterial infection identified in 14 of the 17 RSV positive infants who had a serious bacterial infection. Infants who were RSV positive had a UTI risk of 5.4% compared to 10.1% in RSV negative infants (RR = 0.6 95% CI 0.3-0.9%).

APPLICABILITY: This study was conducted in 8 pediatric emergency department in different areas of the U.S. making it largely generalizable to most patients in the ED setting.

AUTHOR'S CONCLUSION: "The febrile infants with RSV infections, however, had clinically important rates of UTIs and, to a lesser extent bacteremia. Thus, it seems that one cannot necessarily obviate urine and blood testing in these febrile infants on the basis of RSV status alone."

POTENTIAL IMPACT: Though there is a statistically significant reduction in the risk of serious bacterial infection in the RSV positive infants there remains a significant risk and the presence of RSV infection does not definitively preclude a concomitant serious bacterial infection. Continued evaluation for serious bacterial infection and in particular for urinary tract infection is warranted in febrile infants less than 60 days old. Most physicians would need the risk to be significantly lower before they would consider only performing RSV testing. Whether a blood culture or lumbar puncture is necessary in the RSV positive patient with a normal urinalysis remains unanswered.

FEBRILE NEONATE:
ROCHESTER CRITERIA

In febrile neonates, less than 3 months of age, do history, examination and laboratory parameters ("Rochester Criteria") accurately identify those at low risk for a serious bacterial infection?

Michael Mojica, M.D.
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Dagan R, Powell KR, Hall CB, Menegus MA.

IDENTIFICATION OF INFANTS UNLIKELY TO HAVE SERIOUS BACTERIAL INFECTION ALTHOUGH HOSPITALIZED FOR SUSPECTED SEPSIS.

J Pediatr. 1985 Dec;107(6):855-60.
PubMed ID: 4067741

STUDY DEFINITIONS	
POPULATION	Inclusion: 0-3 months Exclusion: Prematurity, perinatal complications, previous or underlying illness, antibiotics prior to evaluation Setting: Single Children's Hospital ED, 1/1982-6/1984
RULE PARAMETERS	Sepsis Workup: Complete blood count with differential, urinalysis, blood, cerebrospinal fluid, urine culture, CSF cell count, protein and glucose Physical examination performed and documented by a pediatric resident, Viral testing July-November: Throat swab. stool or rectal swab, CSF, and blood. November-June: Nasopharyngeal/throat swab, stool or rectal swab, and CSF. December-May: Nasal specimens for respiratory syncytial virus and influenza. Low Risk for Serious Bacterial Infection 1. No examination findings consistent with soft tissue, skeletal, or ear infection 2. Normal WBC: WBC 5,000-15,000/mm^3 3. Normal Differential: < 1,500 Bands/mm^3 4. Normal Urinalysis: < 10 White blood cells/high-power field in centrifuged urine
REFERENCE STANDARD	Serious Bacterial Infections: Bacteremia, meningitis, cellulitis, osteomyelitis, gastroenteritis or urinary tract infection. CSF Pleocytosis: ≥ 20 cells/mm^3 if < 30 days, > 10 cells/mm^3 if > 30 days. Pneumonia: Positive findings on chest roentgenogram Urinary Tract Infection: >10^5 colonies/ml of a single organism in the urine.
OUTCOME	Rule Characteristics
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. Parameters were included based on the investigators experience and existing literature. There were limited to those that were simple, objective and available at the time of disposition decision. These included: physical examination findings, white blood cell count and differential and urinalysis.
Were all important predictors present in significant proportion of the study population?	Unclear. The proportion of the patients with exam and WBC criteria who were at high risk are presented in Table 1 and Table IV. The proportion of the predictors in low risk infants is not presented.
Were the outcome event and predictors clearly defined?	Yes. Specific criteria for each parameter are presented as well as a clear definition of serious bacterial infection.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Yes. The outcome of serious bacterial infection was primarily defined by the presence of bacterial cultures. It is unclear if those reviewing the culture results were aware of the presence of the predictors though it is unlikely that knowledge of the predictors would influence the assessment of the outcome. However, cellulitis was also considered a serious bacterial infection and laboratory parameters were likely interpreted in this context.
Was the sample size adequate (including an adequate number of outcome events)?	Unclear. The study included a total of 233 patients of which 23 (9.9%) had a serious bacterial infection. In general, 10 outcomes are required for each variable included in a rule derived by logistic regression. Since there are 4 predictors, the study would have required 40 patients with a serious bacterial infection

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

N = 233, 61% white, 25% black, 12% Hispanic
Mean 38 days of age (range 4-89 days),
< 30 days (39%), 31-60 days (46%), > 60 days (15%)

	SERIOUS BACTERIAL INFECTION		
	YES	NO	
HIGH RISK	22	67	89
LOW RISK	1	143	144
	23	210	233

Prevalence of SBI: 23/233 = 9.9%
Sensitivity: 22/23 = 95.7%, 95%CI (79, 99.2%)
Specificity: 143/210 = 68.1%, 95% CI (61.5, 74%)
Predictive Value (+) Rule: 22/89= 24.7%, 95% CI (16.9, 34.6%)
Predictive Value (-) Rule: 143/144= 99.3, 95% CI (96.2, 99.9%)
Likelihood Ratio (+) Rule: (22/23)/(67/210) = 3, 95% CI (2.42, 3.72)
Likelihood Ratio (-) Rule: (1/23)/(143/210)= 0.06, 95% CI (0.009, 0.44)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

62 % (144/233) met criteria for low risk of serious bacterial infection. Theoretically, these patients could not be treated with antibiotics and/or discharged with close clinical follow-up though the authors clearly state that they do not make these recommendations.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

No. There was not an internal validation cohort of the study results.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (See Appendix)	☐ I ☐ II ☐ III ? ■ IV This is a difficult rule to classify. At best, it would be considered a level IV rule. Level IV rules have been derived only or validated only in split samples, large retrospective databases or by statistical methods. Level IV rules require further validation before they can be applied clinically. However, this rule was not statistically derived. The rule was instead assembled from potential predictors with predefined cutoffs. It may be unfair to apply the rule classification scheme to a study that pre-dated clear methodologic standards for clinical decision rules.
Does the rule make clinical sense?	Yes. Those with physical exam findings consistent with a bacterial infection and those with a positive urinalysis or those with elevated biomarkers (WBC and absolute band count) would be expected to have a higher risk of serious bacterial infection.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. The laboratory parameters should be reproducible. There was however, no measure of inter-rater reliability for the physical examination finding which were determined by resident physicians.
Is the rule applicable to the patients in my practice?	The study population was from a single institution with a much higher proportion of Caucasian patients then in our population. In addition, a higher proportion of patients had physical examination finding consistent with bacterial infection, those who were ill appearing and those who did not have a fever were included in the study population. These are not typically patients we would consider at low risk of serious bacterial infection. The rate of serious bacterial infection in the population is similar to that typically presented in the literature.
Will the rule results change my management strategy?	Yes. Over 30 years after publication it can be said that this study's result started the process of identifying febrile neonates at low risk of serious bacterial infection that resulted in the selective test and admission approach that is utilized today.
What are the benefits of applying the rule to my patients?	The potential benefits of applying the Rochester Criteria is a reduction in admission or admission without antibiotics for those at low risk of serious bacterial infection.
What are the risks of applying the rule to my patients?	The primary risk is in sending home or not treating with antibiotics a patient with a serious bacterial infection. The sensitivity of the rule was 95.7%, 95%CI (79, 99.2%). The low number of patients in the study results in a very wide confidence interval. Potentially 21% of the patients with a serious bacterial infection could be missed by the rule based on the lower limit of the 95% confidence interval of 79%.

CLINICAL BOTTOM LINE

BACKGROUND: At the time this study was published the standard practice was to complete a full sepsis evaluation and admit all febrile neonates less than 2-3 months of age for antibiotics pending culture results. Approximately 90% of infants who were admitted did not have a serious bacterial infection. Those admitted were at risk for nosocomial infections, complication such as intravenous catheter infiltration and antibiotic related adverse events. If a cohort of infants at very low risk of serious bacterial infection could be identified they could benefit from less invasive testing, antibiotic treatment and fewer admissions.

CLINICAL QUESTION: In febrile neonates, less than 3 months of age, do history, examination and laboratory parameters (the “Rochester Criteria”) accurately identify those at low risk for a serious bacterial infection?

DESIGN/RISK OF BIAS: The authors sought to identify simple and objective criteria that would be available at the time of clinical decision making. This was a retrospective cohort of 233 neonates admitted for intravenous antibiotics pending the results of a cultures. 9.9% of patients had a serious bacterial infection though a breakdown of which infections were present, other than bacteremia, and the organisms responsible were not provided. No temperature cutoff was specified. Some infants were afebrile, others were not well appearing and 8.6% of infants (22% of those with a serious bacterial infection) had a physical examination consistent with a bacterial infection.

There is a potential for verification bias. Reference standard testing was not obtained on all patients. Chest radiographs were obtained for 74% and the CSF cell count was interpretable in 87% of patients. Systemic antibiotics were given to 86% of patients including all that had a serious bacterial infection.

This was not a derivation of a clinical decision rule in that a regression analysis was not used to identify independent predictors of serious bacterial infection. Potential predictors were chosen based on clinical experience and the existing literature. In addition, the cutoffs of continuous predictors were pre-defined. The rule does not specify a course of action such as those at low risk of serious bacterial infection do not require antibiotics or admission.

PRIMARY RESULTS: The rule parameters correctly identified the majority of patients with a serious bacterial infection (Sensitivity 95.7%, 95%CI (79, 99.2%), Predictive Value of a Negative Rule 99.3, 95% CI (96.2, 99.9%)). The rule parameters did not perform as well identifying those without a serious infection (Specificity 68.1%, 95% CI (61.5, 74%), Predictive Value of a positive rule of 24.7%, 95% CI (16.9, 34.6%)). The rule essentially divided a population with a 9.9% risk of serious bacterial infection into a low risk group with a 0.7% risk of serious bacterial infection (1 - Predictive Value of a Negative Rule 99.3%, 95% CI (96.2, 99.9%)) and a high-risk group with a 24.7% risk of serious bacterial infection. (Predictive Value of a Positive Rule = 24.7%, 95% CI (16.9, 34.6%)).

68.1% (144/233) met criteria for low risk of serious bacterial infection. Theoretically, these patients could not be treated with antibiotics or treated with antibiotics and discharged with close clinical follow-up. Alternatively, they could be admitted without antibiotics for observation.

Age, temperature and signs and symptoms did not distinguish between those with and without serious bacterial infection. Viral infection was more common in those without serious bacterial infection (70% vs 41%, $p < 0.0005$). However, 17.5% (4/23) of those with a serious bacterial infection also had a viral infection identified by testing. Viral infection was also more common than bacterial infection in the high-risk group.

APPLICABILITY: The study population was from a single institution with a much higher proportion of Caucasian patients then in our population. However, the rate of serious bacterial infection in the study population is similar to that typically presented in the literature. In addition, a higher proportion of patients had physical examination finding consistent with bacterial infection, were ill appearing and did not have a fever. These are not typically patients we would consider at low risk of serious bacterial infection. Though the majority of the criteria were objective laboratory values. Inter-rater reliability for physical examination findings were not presented.

This is a difficult rule to classify. At best, it would be considered a level IV rule. Level IV rules have been derived only or validated only in split samples, large retrospective databases or by statistical methods. Level IV rules require further validation before they can be applied clinically. However, this rule was not statistically derived. The rule was instead assembled from potential predictors with predefined cutoffs. It may be unfair to apply the rule classification scheme to a study that pre-dated clear methodologic standards for the derivation of a clinical decision rule.

AUTHOR'S CONCLUSION: "We conclude that previously healthy infants younger than 3 months with an acute illness are unlikely to have serious bacterial infection if they have no findings consistent with ear, soft tissue, or skeletal infections and have normal white blood cell and band form counts and normal urine findings."

POTENTIAL IMPACT: 30 years after the publication of this landmark study we are still working to refine the approach to identifying appropriate predictors of low risk of serious bacterial infection in the febrile neonate as the epidemiology of disease evolves and new diagnostic test become available.

APPENDIX: ROCHESTER CRITERIA

ROCHESTER CRITERIA: LOW RISK FOR SERIOUS BACTERIAL INFECTION	
History	0-3 months
	Full term (Not premature)
	No perinatal complications
	No previous or underlying illness,
	No antibiotics prior to evaluation
Examination	No examination findings consistent with soft tissue, skeletal, or ear infection
Laboratory	WBC: 5,000-15,000/mm^3
	Absolute band count < 1,500 band/mm^3
	Urinalysis: < 10 white blood cells/high-power field in a centrifuged urine

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

FEBRILE NEONATE:
STEP-BY-STEP RULE VALIDATION

In febrile infants, less than 90 days of age, does the “Step-by-Step” approach when compared to the Rochester Criteria and the Lab Score adequately distinguish between those with and without invasive bacterial infections (bacteremia and meningitis) and non-invasive bacterial infections (primarily urinary tract infections)?

Michael Mojica, M.D.
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Gomez B, Mintegi S, Bressan S,
Da Dalt L, Gervaix A, Lacroix L;

VALIDATION OF THE STEP-BY-STEP APPROACH
IN THE MANAGEMENT OF YOUNG FEBRILE INFANTS

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STUDY DEFINITIONS	
POPULATION	Inclusion: Infants < 90 days, fever without a source (temperature at home or ED ≥ 38°C), normal examination, no respiratory signs/symptoms or diarrhea. Exclusion: 1. Clear source of fever by history and/or examination 2. No fever in the ED and fever at home assessed only by touch 3. Absence of rule tests: Blood culture, urine culture, CRP, WBC, Procalcitonin 4. Refusal of consent Setting: 11 Pediatric Emergency Departments (Europe), 9/2012-8/2014
RULES (See appendix)	1. Step-by-Step Approach: Low, intermediate and high risk (See appendix) 2. Rochester Criteria: Low risk, not low risk 3. Lab Score: Low risk, not low risk
REFERENCE STANDARD	Invasive Bacterial Infection: (+) Blood culture and/or (+) CSF culture Non-invasive Bacterial Infection: (+) urine culture (catheterized or suprapubic), Telephone follow up within 1 month. If this was not successful electronic registries and public health system were reviewed
CO-INTERVENTIONS	Lumbar puncture, antibiotic administration and the disposition decision was at the discretion of the treating provider
OUTCOME	Rule characteristics
DESIGN	Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were the patients chosen in an unbiased fashion and do they represent a wide spectrum of severity of disease?	Yes. Inclusion and exclusion criteria and demographic characteristics suggest an appropriate spectrum of disease severity. The study enrolled 2,185 patients at 11 European centers.
Was there a blinded assessment of the criterion standard for all patients?	Yes. The criterion standard for the study was invasive bacterial illness defined as a positive blood or urine culture. Clinical and laboratory parameters were assessed prior to the availability of culture results. Prior knowledge of the predictor variables wound not influence the culture results.
Was there an explicit and accurate interpretation of the predictor variables and the actual rule without knowledge of the outcome?	Unclear. 5 of 6 of the predictors in the step-by-step rule are objective (age and 4 laboratory results). The first predictor “abnormal pediatric assessment trial/ill appearing” is subjective. No further description of how this was defined and no measure of inter-rater reliability for this predictor was provided.
Was there 100% follow up of those enrolled?	Unclear. The authors state that telephone follow up occurred within 1 month or hospital and public registries were searched. The proportion available for phone follow up was not provided. This is important. While all patients included had both a urine and blood culture only 27.4% of those enrolled had a lumbar puncture performed.

WHAT ARE THE RESULTS?

DEMOGRAPHIC CHARACTERISTICS

N = 2,185, median age 47 days
Well appearing: 87.7%
Previously healthy: 85.9%
Lumbar Puncture: 27.4%
Antibiotics: 49%
Admitted: 58.5%
All Bacterial Infection: 504/2,185 (23.1%)
Invasive Bacterial Infection: 87/2,185 (3.9%)
Non-Invasive Bacterial Infection: 417/2,185 (19.1%)
(UTI accounted for 98.1% of Non-Invasive Infections)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

DECISION RULE	SENSITIVITY	PREDICTIVE VALUE NEGATIVE RULE
Step-by-Step	92.0% (84.3, 96%)	99.3% (98.5, 99.7%)
Rochester	81.6% (72.2, 88.4%)	98.3% (97.3, 99.0%)
Lab Score	59.8% (49.3, 69.4%)	98.1% (97.3, 98.6%)

Sensitivity and the predictive value of a negative rule were highest for the Step-by-Step Rule

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

Specificity and predictive value of a positive rule were highest for the Lab Rule but it had the lowest sensitivity and predictive value of a negative rule. This illustrate the inherent trade-off of sensitivity and specificity. Decision rule prioritize a low risk for missing disease (a high sensitivity and predictive value of a negative rule).

DECISION RULE	SPECIFICITY	PREDICTIVE VALUE POSITIVE RULE
Step-by-Step	46.9% (44.8, 49%)	6.7% (5.4, 8.3%)
Rochester	44.5% (42.4, 46.6%)	5.7% (4.6, 7.2%)
Lab Score	84% (82.4, 85.5%)	13.4% (10.4, 17.2%)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

Proportion of patients classified as low risk
Step-by-Step: 45.3%,
Rochester: 43,4%,
Lab Score: 82.2%

DECISION RULE	LOW RISK IBI + NON IBI	LOW RISK IBI*	LOW RISK NON-IBI
Step-by-Step	1.1% (0.5, 1.8%)	0.7% (0.2, 1.2%)	0.4% (0, 0.8%)
Rochester	2.1% (1.2, 3.0%)	1.6% (0.9, 2.5%)	0.4% (0, 0.8%)
Lab Score	10.8% (9.4, 12.3%)	1.9% (1.3, 2.6%)	8.8% (7.6, 10.2%)

*There was a statistically significant lower rate of invasive bacterial infection (IBI) for the low risk criteria of the Step-by step rule compared to both the Rochester Criteria and Lab Score.

The impact of the rules is dependent on base baseline rate of admission. The Lab score could reduce admission by 82.2% but at the expense missing a high number of patients with serious illness. The Step-by-Step and Rochester rules could decrease resource utilization by approximately the same amount but with the Step-by-Step rule missing fever patients.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see Appendix)	☐ I ■ II ☐ III ☐ IV This a stage II clinical decision rule. The rule was validated in 1 large, multicenter prospective study including a broad spectrum of patients. An impact analysis has not been completed. Stage II rules can be used in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve.
Does the rule make clinical sense?	Yes. The parameters of the rule make sense. Included in the rule are clinical parameters (clinical appearance and age) and laboratory parameters (procalcitonin, c-reactive protein, white blood cell count, and absolute neutrophil count). These parameters have all been previously assessed to be associated with the risk of bacterial infection.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. 5 of the 6 predictors in the Step-by-Step rule are objective (age and 4 laboratory results). The first predictor “abnormal pediatric assessment trial/ill appearing is subjective. No further description of how this was defined and no measure of inter-rater reliability for this predictor was provided. As the derivation study was retrospective there was no opportunity to measure inter-rater reliability.
Is the rule applicable to the patients in my practice?	Unclear. The study demonstrated a much higher rate of both invasive bacterial infection (3.9%) and non-invasive bacterial infection (19.1%) than that typically seen in U.S. studies (1-2% and 10-12% respectively). It is unclear if this represents selection bias or a population with higher rate of infection. One of the exclusion criteria was the absence of tests required by the Step-by-Step rule (Blood culture, urine culture, CRP, WBC, Procalcitonin). 273/2458 (11.1%) of patients whose parents consented to the study were excluded for “lacking any mandatory data”. If sicker patients were more likely to have all required testing performed then this could account for the higher rates of invasive and non-invasive bacterial infections in the study population.
Will the rule results change my management strategy?	No. Until Procalcitonin is available in a timely manner in our Emergency department the Step-by Step rule cannot be applied.
What are the benefits of applying the rule to my patients?	The Step-by-Step rule is similar to the Rochester criteria in that it classified a near identical proportion of patients as low risk (45.3% vs 43.4%). However, the Step-by-step rule had a statistically significant lower rate of missed invasive bacterial infection in those classified as low risk (0.7% vs 1.6%). The rate of missed non-invasive bacterial infection in those classified as low risk were identical (0.4% vs 0.8%)). Low risk patients could benefit by a lower rate of lumbar puncture, antibiotic administration and admission. 54.7% would be classified as not low risk and would be admitted. This is 3.8% lower than the study admission rate of 58.5%.

What are the risks of applying the rule to my patients?	The sensitivity and negative predictive values for each of the rules reveal that a small proportion of patients classified as low risk could have both invasive and non-invasive bacterial infections. Non-treatment of these patients can result in serious morbidity and mortality. For every 312 patients evaluated by the Step-by-Step rule, 1 patient with an invasive bacterial infection could be missed.In addition, application of the Step-by-Step rule could increase the rates of lumbar puncture and antibiotic administration if all patients who were not classified as low risk had a lumbar puncture and were treated. Since 45.3% were considered low risk, 54.7% would be classified as not low risk and could have these interventions. The actual rate of lumbar puncture (27.4%) and antibiotic administration (49%) were lower in the study population.

CLINICAL BOTTOM LINE

BACKGROUND: The management of the febrile neonate remains an area of considerable debate. Despite multiple published decision rules (Rochester, Boston and Philadelphia criteria), variability exists in the evaluation and management of these patients. As the epidemiology of serious bacterial infection has evolved primarily due to vaccination for H influenzae and S Pneumoniae and with the availability of new biomarkers, alternative approaches should be evaluated. The ability to identify a subgroup of febrile neonates at low risk for serious bacterial infection could potentially reduce the frequency of lumbar puncture, antibiotic administration and admission for these patients. This should be balanced by the risk of missed bacterial infections with the potential for serious morbidity and mortality.

CLINICAL QUESTION: In febrile infants, less than 90 days of age, what are the test characteristics of the “Step-by-Step” approach when compared to the Rochester Criteria and the Lab Score in identifying invasive bacterial infections (bacteremia and meningitis) and non-invasive bacterial infections (primarily urinary tract infections)?

DESIGN/RISK OF BIAS: This was a prospective validation of a previously derived clinical decision rule (Mintegi, Emerg Med J., PubMed ID: 23851127). The analysis included 2,185 febrile infants. The step by step rule included both clinical and laboratory criteria. The criteria included, clinical status, age, leukocysturia and acute phase reactants (C reactive protein, procalcitonin and absolute neutrophil counts). The performance of the Step-by-Step rule (See appendix) was compared to that of the Rochester Criteria and the Lab Rule. The Boston and Philadelphia criteria were not compared because they recommend lumbar puncture in all patients and this was not the existing approach at the study institutions.

The comparison to the Rochester Criteria may not be legitimate. The absolute band count required by the Rochester criteria was not available in all study centers and may have affected performance of the Rochester Criteria. Typically, the addition of another criteria will raise the sensitivity at the expense of specificity. In addition, the Rochester criteria were applied to all children less than 90 days in the study while the Step-by-Step rule excluded patients less than 21 days. Children less than 28 days have a higher prevalence of serious bacterial infection. A higher pretest probability of disease results in higher post-test probability of disease. This manifests in the test characteristics as a high predictive value of a positive test and a low predictive value of a negative test. The sensitivity and predictive value of a negative test of the Rochester Criteria may be higher than presented in the study.

Finally, the proportion of those who did not have a lumbar puncture and were not available for phone follow-up was not provided. This would be important as the primary outcome of invasive bacterial infection included a positive CSF culture and only 27.4% of the study population had a lumbar puncture performed.

PRIMARY RESULTS: The rates of bacterial infection were: all Bacterial Infection: 23.1% (504/2,185), Invasive Bacterial Infection: 3.9% (87/2,185) and Non-Invasive Bacterial Infection: 19.1% (417/2,185). Urinary tract infections accounted for 98.1% of the non-invasive bacterial infections. The Step-by-Step rule had the highest sensitivity (92.0%, 95% CI (84.3, 96%) and predictive value of a negative rule (99.3%, 95% CI, (98.5%, 99.7%)).
The Step-by-Step Rule would result in a statistically significant lower risk of missed invasive bacterial infection (0.7%, 95% CI (0.2, 1.2%) when compared to the Rochester criteria and Lab Rule.

Low risk patients could benefit by a lower rate of lumbar puncture, antibiotic administration and admission. In addition, application of the Step-by-Step rule could potentially decrease the rate of admission. Since 45.3% were considered low risk, 54.7% would be classified as not low risk and would be admitted. This is 3.8% lower than the study admission rate of 58.5%.

However, application of the Step-by-Step rule could increase the rates of lumbar puncture, antibiotic administration if all patients who were not classified as low risk had a lumbar puncture and were treated. 54.7% would be classified as not low risk and would have these interventions. The study rates of these interventions were significantly lower: Lumbar puncture (27.4%), antibiotic administration (49%).

DECISION RULE	SENSITIVITY	PREDICTIVE VALUE NEGATIVE RULE	SPECIFICITY	PREDICTIVE VALUE POSITIVE RULE
Step-by-Step	92.0% (84.3, 96%)	99.3% (98.5, 99.7%)	46.9% (44.8, 49%)	6.7% (5.4, 8.3%)
Rochester	81.6% (72.2, 88.4%)	98.3% (97.3, 99.0%)	44.5% (42.4, 46.6%)	5.7% (4.6, 7.2%)
Lab Score	59.8% (49.3, 69.4%)	98.1% (97.3, 98.6%)	84% (82.4, 85.5%)	13.4% (10.4, 17.2%)

RISK OF INFECTION IN PATIENTS CLASSIFIED AS LOW RISK			
Decision Rule	Invasive + Non-Invasive Bacterial Infection	Invasive Bacterial Infection	Non-Invasive Bacterial Infection
Step-by-Step	1.1% (0.5, 1.8%)	0.7% (0.2, 1.2%)	0.4% (0, 0.8%)
Rochester	2.1% (1.2, 3.0%)	1.6% (0.9, 2.5%)	0.4% (0, 0.8%)
Lab Score	10.8% (9.4, 12.3%)	1.9% (1.3, 2.6%)	8.8% (7.6, 10.2%)

4 of the 7 patients missed by the Step-by-Step Rule were 22-28 days. Febrile neonates typically present early after fever onset. In this study, the median duration of fever was 5 hours. Fever was measured for the first time in the ED in 3 of the 7 missed patients and within 1 hours in 3 others. Though Procalcitonin is more rapidly elevated than CRP or WBC, the elevation may not be rapid enough for those presenting very early after fever onset.

APPLICABILITY: There are a number of applicability issues that would need to be addressed prior to generalizing the study's results. 5 of the 6 predictors in the Step-by-Step rule are objective (age and 4 laboratory results). The first predictor "abnormal pediatric assessment trial/ill appearing" is subjective. No measure of inter-rater reliability for this predictor was provided. As the derivation study was retrospective there was no opportunity to measure inter-rater reliability as well.

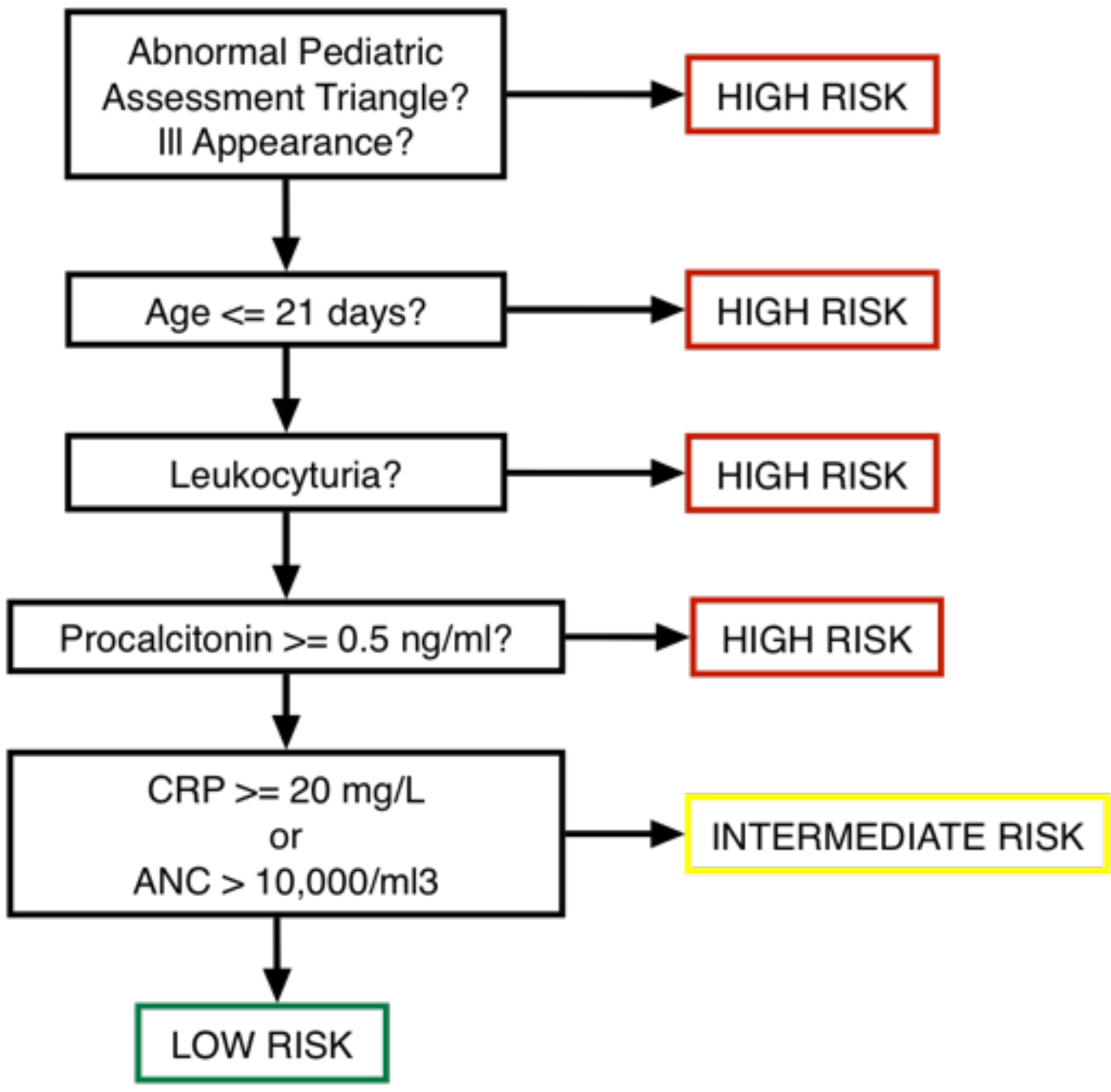
In addition, the study demonstrated a much higher rate of both invasive bacterial infection (3.9%) and non-invasive bacterial infection (19.1%) than that typically seen in U.S. studies (1-2% and 10-12% respectively). It is unclear if this represents selection bias or a population with higher rate of infection. Until Procalcitonin is available in a timely manner in our Emergency department the Step-by Step rule cannot be applied. One of the exclusion criteria was the absence of tests required by the Step-by-Step rule. 11.1% of patients whose parents consented to the study were excluded for "lacking any mandatory data". If sicker patients were more likely to have all required testing performed then this could account for the higher rates of invasive and non-invasive bacterial infections in the study population.

The Step-by-Step rule is a stage II clinical decision rule. The rule was validated in 1 large, multicenter prospective study including a broad spectrum of patients. An impact analysis has not yet been completed. The rule can be used in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve.

AUTHOR'S CONCLUSION: "The Step-by-Step approach revealed a high sensitivity, being more accurate than the Rochester criteria and the Lab-score at identifying children at low risk of IBI, and appears to be a useful tool for the management of the febrile infant in the ED. However, as no perfect tool exists, the Step by Step is not 100% sensitive and physicians should use caution especially when assessing infants with a very short fever evolution. For this subgroup of patients, we strongly advise for an initial period of close observation and monitoring in the ED, even when all the complementary test values are normal."

POTENTIAL IMPACT: The Step-by-Step Rule had a higher sensitivity and predictive value of a negative rule and a lower risk of missed invasive bacterial infection than the Rochester Criteria and Lab rules. There are a number of validity and applicability concerns that would need to be addressed prior to application of the rule. Use of any of the febrile neonate decision rule will depend on an individual clinician's risk aversion. The febrile neonate in the emergency department presents an opportunity for shared decision making with the parents and the primary care provider. Caution should be taken in applying the rule to those 22-28 days or age and those who present within a few hours of fever onset as these patients accounted for the majority of patients with a missed bacterial infection.

APPENDIX: STEP-BY-STEP RULE



APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

SEE ALSO:

STEP BY STEP RULE (DERIVATION)
Mintegi S, Bressan S, Gomez B, Da Dalt L, Blázquez D, Olaciregui I, de la Torre M, Palacios M, Berlese P, Benito J.
Accuracy of a sequential approach to identify young febrile infants at low risk for invasive bacterial infection.
Emerg Med J. 2014 Oct;31(e1):e19-24. PubMed ID: 23851127

ROCHESTER CRITERIA
Dagan R, Powell KR, Hall CB, Menegus MA.
Identification of Infants Unlikely to Have Serious Bacterial Infection Although Hospitalized for Suspected Sepsis.
J Pediatr. 1985 Dec;107(6):855-60., PubMed ID: 4067741

LAB SCORE RULE
Lacour AG, Zamora SA, Gervaix A.
A Score Identifying Serious Bacterial Infections in Children with Fever Without Source.
Pediatr Infect Dis J. 2008 Jul;27(7):654-6., PubMed: 18536624

FEBRILE NEONATE:
URINALYSIS ACCURACY

In febrile (≥ 38 C) neonates less than 60 days of age, what are the test characteristics of urinalysis components (nitrite, leukocyte esterase and pyuria) and the aggregate urinalysis in identifying isolated urinary tract infections and urinary tract infection associated with bacteremia?

Michael Mojica, M.D.
January 2018

Tzimenatos L, Mahajan P, Dayan PS, Vitale M, Linakis JG, Blumberg S, Borgialli D, Ruddy RM, Van Buren J, Ramilo O, Kuppermann N; Pediatric Emergency Care Applied Research Network (PECARN)

ACCURACY OF THE URINALYSIS FOR URINARY TRACT INFECTIONS IN FEBRILE INFANTS 60 DAYS AND YOUNGER

Pediatrics. 2018 Jan 16. pii: e20173068.
PubMed ID: 29339564

STUDY DEFINITIONS	
POPULATION	Inclusion: ≤ 60 days, ≥ 38 C, blood culture obtained, urinalysis obtained, catheterized or suprapubic urine sample culture obtained. Exclusion: Clinical sepsis, prematurity, significant comorbid condition, recent systemic antibiotic use, focal bacterial infections except otitis media. Bacteremia without a UTI, bacteremia with a concurrent UTI by different pathogens Setting: Multicenter, N = 26 Children's Hospital ED's (PECARN), 12/2008-5/2013
TEST	Urinalysis: Individual components Leukocyte esterase: (+) of any amount Nitrites: (+) Pyuria: (+) > 5 WBC/HPF, (-) ≤ 5 WBC/HPF or Nitrite (-) & LE (-) and microscopy was not performed Urinalysis: In aggregate Positive = LE (+) OR Nitrite (+) OR Pyuria (+) Negative = LE (-) AND Nitrite (-) AND (Pyuria (-) or microscopy not preformed)
REFERENCE STANDARD	Primary Analysis: UTI (+): ≥ 50,000 CFU/ml of a known urinary pathogen (catheterized) UTI (+): ≥ 1,000 CFU/ml of a known urinary pathogen (suprapubic) UTI (-): Urine culture (-) OR Contaminant OR Pathogen < CFU/ml threshold Secondary Analysis: UTI (+): ≥ 10,000 CFU/ml of a known urinary pathogen (catheterized) UTI (+): ≥ 1,000 CFU/ml of a known urinary pathogen (suprapubic) UTI (-): Urine culture (-) OR Contaminant OR Pathogen < CFU/ml threshold Contaminants: Known skin or GU flora. e.g. Coagulase negative staph, lactobacillus, Corynebacterium
OUTCOME	Test characteristics of UA components (LE, nitrites, pyuria) and UA in aggregate Stratified by: All with UTI, UTI without bacteremia and UTI with bacteremia Stratified by: Age ≤ 28 days and 29-60 days Stratified by: UTI defined as ≥ 50,000 CFU/ml and defined as ≥ 10,000 CFU/ml
DESIGN	Observational: Prospective Cross-Sectional Study

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. Patients were febrile infants who did not have clinical evidence of sepsis. Urinary tract infection is an occult infection in these patients.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The investigators compared the components of the urinalysis and the aggregate urinalysis to cultures obtained by catheterization or suprapubic aspiration. For a catheterized specimen, a positive culture was defined as ≥ 50,000 CFU/ml or ≥ 10,000 CFU/ml of a known urinary pathogen. For a suprapubic specimen, a positive culture was defined as ≥ 1,000 CFU/ml of a known urinary pathogen.
Were those interpreting the test and reference standard blind to the other results?	Yes. The results of the urinalysis were available prior to the results of the urine culture. Those who interpreted the urine culture by predefined standards may have had knowledge of the urinalysis results though this knowledge would not have affected the interpretation of the objective outcome of positive urine culture.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	Yes. All patients had a urine culture obtained by bladder catheterization of suprapubic aspiration. The definition of a positive urine culture was modified based on the method used to obtain it. A suprapubic aspiration was performed in only 0.2% of the patients.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 4,147

UTI: 289/4,147 = 7%, 95% CI (6.3, 7.8%)(based on UTI definition of ≥ 50,000 CFU/ml)

E Coli (82%), Klebsiella sp. (4.5%) enterococcus sp. (3.1%), Enterobacter sp. (2.8%).

UTI + Bacteremia (those with UTI) = 27/289 = 9.3%, 95% CI (6.2, 13.3%)

UTI + Bacteremia (entire population) = 27/4,147 = 0.7%, 95% CI (0.4, 0.9%)

TEST CHARACTERISTICS: UA COMPONENTS & AGGREGATE UA

	UTI (n=289)		UTI + BACTEREMIA (n=27)	
	SENSITIVITY	SPECIFICITY	SENSITIVITY	SPECIFICITY
Leukocyte (LE)	92% (88, 95%)	96% (95, 96%)	100% (87, 100%)	96% (95, 96%)
Nitrites	38% (32, 44%)	99% (99, 100%)	41% (22, 61%)	99% (99, 100%)
> 5 WBC/HPF	82% (77, 87%)	94% (93, 94%)	77% (55, 92%)	94% (93, 94%)
Aggregate UA*	94% (90, 96%)	91% (90, 91%)	100% (87, 100%)	91% (90, 91%)
*Aggregate UA (+) if LE (+) OR Nitrite (+) OR Pyuria (> 5 WBC/HPF)				

TEST CHARACTERISTICS: AGGREGATE UA BY AGE

	ALL (4,147)	≤ 28 DAYS (1,296)	29-60 DAYS (2,851)
Sensitivity	94% (91, 97%)	97% (92, 99%)	93% (88, 96%)
Specificity	91% (90, 91%)	90% (88, 91%)	91% (90, 92%)
PV (+) Test	43% (39, 47%)	50% (43, 56%)	39% (34, 44%)
PV (-) Test	100% (99, 100%)	100% (99, 100%)	100% (99, 100%)
LR (+) Test	10.0 (9.0, 11.1)	9.3 (9.0, 11.1)	10.3 (9.1, 11.7)
LR (-) Test	0.06 (0.04, 0.10)	0.04 (0.01, 0.09)	0.08 (0.05, 0.14)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Yes. The interpretation of the urinalysis and its components is objective.
Are the study results applicable to the patients in my practice?	Yes. This was a multicenter study including patients from 26 pediatric emergency department emergency departments. The rate of UTI and UTI with bacteremia are similar to previously published studies. Therefore, the study's results are likely generalizable to our population.
Will the test results change my management strategy?	Yes. The urinalysis is already used to risk stratify febrile neonates. This study demonstrated improved test characteristics if the UA and its components.
Will patients be better off as a result of the test?	Yes. A high sensitivity indicates that fewer patients with a UTI will be missed. These patients can be targeted for admission and treatment. A high specificity that fewer patients will be miss identified as having a UTI when they do not. If these patients are otherwise low risk by clinical and laboratory criteria they could potentially be discharged without antibiotics.

CLINICAL BOTTOM LINE

BACKGROUND: Urinary tract infection (UTI) if the most common infection in well appearing febrile infants less than 60 days of age accounting for approximately 80-90% of serious bacterial infections in this age group. 60% of febrile infants and toddlers with UTI will have evidence of pyelonephritis on DMSA renal scans (Hoberman, Pediatrics 1999, PubMed ID: 10390264). UTI is also responsible for a proportion of patients with both bacteremia and meningitis in this age group.

The reported test characteristics for a urinalysis have varied greatly in prior studies. This is likely due in part to different definitions of what constitutes a positive urinalysis and urine culture. In has been thought the infant have a blunted inflammatory response to UTI making leukocyte esterase and pyuria less sensitive as a marker of UTI then they are in older patients. In addition, children urinate frequently, giving nitrites less time to accumulate in the urine. A recent study found the test characteristics of the urinalysis in patients with UTI and bacteremia to be better that previously reported (Schroeder, Pediatrics 2015, PubMed ID: 26009628). The authors studied this population to eliminate the possibility of including patients with asymptomatic bacteriuria. The primary concern with this study is that of spectrum bias, which is the urinalysis test characteristics may be better in those with both a positive urine culture and a positive blood culture when compared to those with only a positive urine culture.

CLINICAL QUESTION: In febrile (≥ 38 C) neonates less than 60 days of age, what are the test characteristics of urinalysis components (nitrite, leukocyte esterase and pyuria) and the aggregate urinalysis in identifying isolated urinary tract infections and urinary tract infection associated with bacteremia?

DESIGN/RISK OF BIAS: This was well design, multicenter, prospective cross-sectional study that was a planned secondary analysis of the PECARN bio signature study. The study included febrile infants less than or equal to 60 days of age in which a urine culture was obtained by bladder catheterized or suprapubic aspiration. The study excluded those with clinical evidence of sepsis, those with a history of prematurity, significant comorbid condition, or recent systemic antibiotic use, and those with a focal bacterial infection on examination other than otitis media. There were no major validity concerns.

PRIMARY RESULTS: The study included 4,147 patients of which 7%, 95% CI (6.3, 7.8%) had a UTI (based on a UTI definition of ≥ 50,000 CFU/ml). The primary pathogens were E Coli (82%), Klebsiella sp. (4.5%) enterococcus sp (3.1%) and Enterobacter sp. (2.8%). Bacteremia was present in 9.3%, 95% CI (6.2, 13.3%) of those with a UTI and 0.7%, 95% CI (0.4, 0.9%) of the population as a whole (patients with bacteremia not related to a UTI were excluded from the study). Infants with a UTI were statistically more likely to be female, ≤ 28 days of age and have a higher median temperature, white blood cell count and absolute neutrophil counts.

The sensitivity of nitrites was poor. This is consistent with prior evidence. The sensitivity of leukocyte esterase (LE) in patients with an isolated UTI was 92%, 95% CI (88, 95%) and in patients with UTI and bacteremia was 100%, 95% CI (87, 100%). These are described as excellent by the authors though the lower limits of the 95% confidence intervals leave room for missing patients with UTI. The sensitivity of the aggregate UA was high: 94%, 95% CI (90, 96%) in those with isolated UTI and 100%, 95% CI (87, 100%) with a UTI and bacteremia. The specificities of each of the UA components and the aggregate UA were high. The test characteristics did not vary considerably when stratified by age though. Additionally,

the test characteristics did not vary considerably when UTI was defined as ≥ 10,000 CFU/ml though the sensitivity of the aggregate UA was lower at 87%, 95% CI (83, 90%) compared to 94%, 95% CI (90, 96%) when UTI was defined as ≥ 50,000 CFU/ml.

TEST CHARACTERISTICS: UA COMPONENTS & AGGREGATE UA				
	UTI ONLY (n=289)		UTI + BACTEREMIA (n=27)	
	SENSITIVITY	SPECIFICITY	SENSITIVITY	SPECIFICITY
Leukocyte (LE)	92% (88, 95%)	96% (95, 96%)	100% (87, 100%)	96% (95, 96%)
Nitrites	38% (32, 44%)	99% (99, 100%)	41% (22, 61%)	99% (99, 100%)
> 5 WBC/HPF	82% (77, 87%)	94% (93, 94%)	77% (55, 92%)	94% (93, 94%)
Aggregate UA*	94% (90, 96%)	91% (90, 91%)	100% (87, 100%)	91% (90, 91%)
Aggregate UA (+) = LE (+) OR Nitrite (+) OR Pyuria (> 5 WBC/HPF)				

TEST CHARACTERISTICS: AGGREGATE UA BY AGE			
	ALL (4,147)	≤ 28 DAYS (1,296)	29-60 DAYS (2,851)
Sensitivity	94% (91, 97%)	97% (92, 99%)	93% (88, 96%)
Specificity	91% (90, 91%)	90% (88, 91%)	91% (90, 92%)
PV (+) Test	43% (39, 47%)	50% (43, 56%)	39% (34, 44%)
PV (-) Test	100% (99, 100%)	100% (99, 100%)	100% (99, 100%)
LR (+) Test	10.0 (9.0, 11.1)	9.3 (9.0, 11.1)	10.3 (9.1, 11.7)
LR (-) Test	0.06 (0.04, 0.10)	0.04 (0.01, 0.09)	0.08 (0.05, 0.14)

APPLICABILITY: This was a multicenter study including patients from 26 pediatric emergency department emergency departments. The rate of UTI and UTI with bacteremia are similar to previously published studies. Therefore, the study's results are likely generalizable to this population and setting. It is unclear why those with bacteremia without a UTI and bacteremia with a different pathogen than a concurrent UTI were excluded. The test characteristics of the entire population of the well appearing febrile neonates would have been helpful.

AUTHOR'S CONCLUSION: "The urinalysis (including any leukocyte esterase, nitrites, or pyuria > 5 WBCs/HPF) is a highly sensitive and specific screening test for UTIs in febrile infants ≤ 60 days old, particularly in those with associated bacteremia. The urinalysis provides valuable and reliable information to clinicians evaluating the youngest febrile infants for serious bacterial infections."

POTENTIAL IMPACT: The study demonstrated good test characteristics of the aggregate urinalysis in the well appearing febrile neonate. Despite the studies large sample size, the lower limits of the 95% confidence intervals for sensitivity leaves room for occasionally missing a patient with a UTI and a negative urinalysis. This has practical implications. The strategy of obtaining a bagged specimen for urinalysis and only catheterizing those with a positive urinalysis may miss patients with UTI. The urinalysis is only one tool in assessing the febrile neonate for serious bacterial infection. It would be helpful to see for example how the urinalysis performs in conjunction with acute phase reactants such as the WBC, ANC, ABC, CRP and procalcitonin.

INFLUENZA:
OSELTAMIVIR

In children and adults who are healthy or with a chronic underlying condition that puts them at higher risk of influenza complications and who have an influenza-like illness, does Oseltamivir when compared to Placebo provide symptom relief and decrease hospitalization and complications without an associated increase in adverse events related to therapy?

Michael Mojica, M.D.
May 2017

Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ.

OSELTAMIVIR FOR INFLUENZA IN ADULTS AND CHILDREN: SYSTEMATIC REVIEW OF CLINICAL STUDY REPORTS AND SUMMARY OF REGULATORY COMMENTS.

BMJ. 2014 Apr 9; 348.
PubMed ID: 24811411

STUDY DEFINITIONS	
POPULATION	Inclusion: Randomized controlled trails, children or adults, healthy prior to exposure or with chronic illness. treatment of influenza-like illness that might be caused by Influenza A or B Exclusion: Randomized controlled trials for which the clinical study reports were not available, immunocompromised patients (e.g. malignancy, HIV). Table 1 describes inclusion and exclusion criteria for the individual studies Setting: Studies published 1998-2004, Conducted on all continents with the exception of Antarctica.
INTERVENTION	Neuraminidase inhibitor (Oseltamivir) by any route
CONTROL	Placebo
OUTCOME	Primary Outcomes: Symptom relief, admission, complications, adverse events. Complications: Pneumonia, bronchitis, otitis media, sinusitis. Stratified by method of diagnosis: Laboratory/radiologically confirmed, clinical diagnosis without confirmation or other (e.g. patient self-report) Sub-analysis of complications classified as serious Harms: Serious adverse events, all adverse events leading to study withdrawal, and all adverse events within a defined body system, common adverse events as defined in the Food and Drug Administration drug labelling Sub-analysis of on-treatment vs off-treatment adverse events Secondary Outcomes: Symptom relapse after finishing treatment, drug resistance, viral excretion, change in antibody titers, mortality.
DESIGN	Systematic Review and Meta-analysis of Clinical Study Reports

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review explicitly address a sensible clinical question?	Yes. The study addressed a specific question for which there was considerable controversy due to the exclusion from prior analyses of manufacturer unpublished data. Explicit definitions of each variable as well as the rationale for classification are provided.
Was the search for relevant studies detailed and exhaustive?	Yes. Publications, registries, correspondence with manufacturers, and review of regulatory documents were used to identify manufacturer funded and non-manufacturer funded clinical trials and their clinical study reports. Updated searches of electronic databases from prior Cochrane reviews on neuraminidase inhibitors in children and in healthy adults was conducted until 7/22/2013. Search strategies presented in a supplemental appendix. An assessment for publication bias was not presented.
Was the risk of bias of the primary studies assessed?	Yes. Extraction of data was based on the CONSORT statement checklist from the clinical trial reports. Trials were only included if they satisfied CONSORT criteria for completeness, internal consistency and external consistency. The Cochrane risk of bias tool was adapted to assess the risk of bias of clinical study reviews. Many of the studies were at significant risk of bias.
Were the selection and assessment of studies reproducible?	Two authors applied the inclusion criteria to the full clinical study reports with disagreements resolved through discussion. Two reviewers independently conducted the data abstraction and quality assessment and a third served as the arbitrator. No measure of inter-rater reliability was presented for study inclusion or study quality

WHAT WERE THE RESULTS?	
Were the results similar from study to study?	Heterogeneity varied with different outcomes and subgroups. I^2 values were used to assess heterogeneity and are included in the tables in the clinical bottom line. The more conservative random effects model was used to combine data.
What are the overall results of the review?	See tables in the clinical bottom line for time to symptom resolution, admission, influenza complications and Oseltamivir adverse events. In general, treatment with Oseltamivir was associated with an earlier time to symptom resolution but not a reduction in admission or influenza complication. However, Oseltamivir was associated with an increased rate of nausea in vomiting in 20-25% of adult patients.
Did the review address confidence in effect estimates	See Tables in the Clinical Bottom Line section for confidence intervals around the reported risk differences and relative risks. In general, the confidence intervals are wider for pediatric results due to the small sample size and wider for rare outcomes.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were all patient-important outcomes considered?	Yes. Multiple efficacy and safety outcomes were included. Many of these were patient oriented.
Are any postulated subgroup effects credible?	Results were reported separately for adults and children. The outcomes or complications and adverse events were analyzed separately for individual outcomes. In addition. a sub-analysis of complications describes as serious or which required study withdrawal was included.
What is the overall quality of the evidence?	The overall quality of the evidence was poor to moderate. Adequate Randomization (43%), Allocation concealment (65%), Blinding of participants and staff (48%), blinding of outcome assessors (83%). The authors report a high risk of bias from missing data. Specific criteria for many of the outcomes was not provided.
Are the benefits worth the costs and potential risks?	For the individual patient, it is unclear that the benefit in terms of reduction in symptoms duration can be offset by the rate of adverse events particularly when no benefits were seen in the rate of admission or serious adverse events. On a societal level, there may not be sufficient justification for the cost of stockpiling Oseltamivir.

CLINICAL BOTTOM LINE

EDITOR'S NOTE: This critical article review will focus on the safety and efficacy of Oseltamivir when used as treatment for influenza. Data presented in the article on prophylactic Oseltamivir are not reviewed.

BACKGROUND: Oseltamivir is recommended by the World Health Organization and the Centers for Disease Control and Prevention. The data which these recommendations are based on did not include unpublished data. The authors succeeded in obtaining the study reports of unpublished trials from Roche the manufacturer of Oseltamivir. This is the first Cochrane review based on all relevant clinical study reports.

CLINICAL QUESTION: In children and adults who are healthy or with a chronic underlying condition that puts them at higher risk of influenza complications and who have an influenza-like illness, does Oseltamivir when compared to Placebo provide symptom relief and decrease hospitalization and complications without an associated increase in adverse events related to therapy?

DESIGN/RISK OF BIAS: This was a well-designed meta-analysis of randomized trials on the efficacy and safety of treatment with Oseltamivir in adults and children with signs and symptoms of influenza-like illness. This meta-analysis includes previously unpublished data by the drug manufacturer. 3,954 adults and 1,329 children were included in the primary analysis. The authors used the clinical study reports (mean of 1,300 pages).

As with any meta-analysis, the quality of the results is limited by the quality of the included studies. The Cochrane risk of bias tool demonstrated several validity concerns including a low proportion with adequate randomization (43%), allocation concealment (65%), blinding of participants and staff (48%) and blinding of outcome assessors (83%).

PRIMARY RESULTS: The use of Oseltamivir for treatment of patients with influenza-like illness resulted in a statistically significant decrease in the time to alleviation of symptoms in adults of 16.8 hours, 95% CI (8.4, 25 hours) and in healthy children of 29.5 hours, 95% CI (11.8, 47.1 hours) but not in children with asthma (5.2 hours, 95% CI (-11.1, 21.4hours). The durability of symptom relief beyond 5 days was not assessed.

TIME TO ALLEVIATION OF SYMPTOMS (FIGURE 3, 4 IN SUPPLEMENT)					
Group	Trials	I^2	Oseltamivir	Placebo	Mean Difference[1] (95% CI)
Adults	11	0%	2,208	1,746	16.8 (8.4, 25) hours[2]
Children: Healthy	1	NA	331	338	29.5 (11.8, 47.1) hours[2]
Children: Asthma	3	0%	333	327	5.2 (-11.1, 21.4) hours
Children: All	4	88%	664	665	8.0 (-17.6, 33.3) hours

[1] Mean Difference (hours) = Oseltamivir – Placebo, [2] Statistically significant difference
GREEN = STATISTICALLY SIGNIFICANT, RED = NOT STATISTICALLY SIGNIFICANT

There was not a statistically significant reduction in admission for children or adults.

ADMISSION (FIGURE 3, 4 IN SUPPLEMENT)					
GROUP	TRIALS	I^2	Oseltamivir	Placebo	Risk Ratio[1] (95% CI)
Adult	10	0%	38/2,663 (1.4%)	32/1,731 (1.8%)	0.92 (0.57, 1.50)
Children	4	0%	12/667 (1.8%)	6/682 (0.9%)	1.92 (0.70, 5.23)

[1] Risk Ratio = Oseltamivir/Placebo, [2] Statistically significant difference
GREEN = STATISTICALLY SIGNIFICANT, RED = NOT STATISTICALLY SIGNIFICANT

There was no statistically significant reduction in complications of therapy in adults including serious complications or those requiring removal from the trial or in the proportion with sinusitis, bronchitis or acute otitis media. There was however a statistically significant reduction in pneumonia in adults of 1%, 95% CI (0.22, 1.49%) though the clinical significance of a 1% reduction with is questionable. There was no statistically significant difference in the rate of pneumonia when trials requiring radiologic confirmation or trials that had a specific data entry point for pneumonia were analyzed.

There was no statistically significant difference in complications of therapy in children including serious complications or those requiring removal from the trial or in the proportion with bronchitis, acute otitis media or pneumonia (Table 4).

COMPLICATIONS (FIGURE 8-15 IN SUPPLEMENT)					
GROUP	TRIALS	I^2	Oseltamivir	Placebo	Risk Ratio[1] (95% CI)
Adult: Sinusitis	11	0%	112/2,694 (4.2%)	64/1,758 (3.6%)	1.03 (0.76, 1.30)
Adult: Bronchitis	11	36%	157/2,694 (5.8%)	161/1,758 (9.2%)	0.75 (0.56, 1.01)
Adult: Otitis	9	0%	25/2,646 (0.9%)	14/1,722 (0.8%)	1.11 (0.57, 2.15)
Adult: Pneumonia	11	0%	27/2,694 (1.0%)	39/1,758 (2.2%)	0.55 (0.33, 0.90)
Adult: Serious[2]	9	0%	13/2,179 (0.6%)	11/1,496 (0.7%)	0.91 (0.40, 2.06)
Child: Pneumonia	4	0%	26/677 (3.8%)	25/682 (3.7%)	1.06 (0.62, 1.85)
Child: Serious[2]	4	0%	8/677 (1.2%)	4/682 (0.6%)	1.98 (0.58, 6.72)
Pneumonia Clear[3]	9	0%	35/1,349 (2.6%)	40/1,365 (2.9%)	0.93 (0.59, 1.47)

GREEN = STATISTICALLY SIGNIFICANT, RED = NOT STATISTICALLY SIGNIFICANT
[1] Risk Ratio = Oseltamivir/Placebo
[2] Complication classified as serious or leading to study withdrawal
[3] Pneumonia: Adult and children with clear diagnostic confirmation capture

Treatment with Oseltamivir was associated with a statistically significant increase in adults of nausea (number need to harm 28, 95% CI (14, 112)) and vomiting (number need to harm 22, 95% CI (14, 42)).

ADVERSE EVENTS (FIGURE 21-26 IN SUPPLEMENT)					
GROUP	TRIALS	I^2	Oseltamivir	Placebo	Risk Ratio[1] (95% CI)
Adult: Nausea	11	43%	304/2,694 (11.3%)	113/1,758 (6.4%)	1.57 (1.14, 2.15)[2]
Adult: Vomiting	11	12%	243/2,694 (9.0%)	56/1,758 (3.2%)	2.43 (1.75, 3.38)[2]
Adult: Diarrhea	11	44%	156/2,694 (5.8%)	124/1,758 (7.1%)	0.67 (0.46, 0.98)
Adult: Cardiac	9	0%	15/2,438 (0.6%)	20/1,505 (1.3%)	0.49 (0.25, 0.97)
Adult: Psych	10	0%	18/2,677 (0.7%)	13/1,749 (0.7%)	0.93 (0.43, 2.03)
Child: Vomiting	4	0%	89/676 (13%)	52/682 (7.6%)	1.70 (1.23, 2.35)

GREEN = STATISTICALLY SIGNIFICANT, RED = NOT STATISTICALLY SIGNIFICANT
1. Risk Ratio = Oseltamivir/Placebo

In adults, the proportion of patients with a four-fold increase in antibody titers was statistically lower in the treatment group (54.3%) compared to the placebo group (58.9%), relative risk 0.92, 95% CI (0.86, 0.97). There was a similar risk difference in children. Treatment group (54.6%) vs placebo group (61.4%), relative risk 0.90, 95% CI, (0.80, 1.0). This may have potential implications for post infection immunity.

APPLICABILITY: There are several factors that limit the generalizability of the study's results. The efficacy of Oseltamivir in children and adults who are being admitted for complications of influenza was not assessed in this study. In addition, the meta-analysis did not assess the efficacy of Oseltamivir in patients presenting after 36-48 hours of illness. This study also did not require confirmation of influenza by testing. This is a pragmatic approach as many patients are treated based on symptoms of an "influenza-like illness" without testing. However, treatment of patients without influenza with Oseltamivir may reduce its apparent efficacy. No conclusions could be made on the effect of Oseltamivir on viral transmission.

AUTHOR'S CONCLUSION: "Given that oseltamivir is now recommended as an essential medicine for the treatment of seriously ill patients or those in higher risk groups with pandemic influenza, the issues of mode of action, lack of sizeable benefits, and toxicity are of concern. This is made worse by the record and stated intentions of governments to distribute oseltamivir to healthy people to prevent complications and interrupt transmission on the basis of a published evidence base that has been affected by reporting bias, ghost authorship, and poor methods.

We believe these findings provide reason to question the stockpiling of oseltamivir, its inclusion on the WHO list of essential drugs, and its use in clinical practice as an anti-influenza drug."

POTENTIAL IMPACT: This meta-analysis, including previously unpublished data, calls into question the efficacy of Oseltamivir in reducing admission or significant complication of influenza in children and adults. In general, treatment with Oseltamivir was associated with an earlier time to symptom resolution but not a reduction in admission or influenza complication. However, Oseltamivir was associated with an increased rate of nausea and vomiting in 20-25% of adults.

For the individual patient, it is unclear that the benefit in terms of reduction in symptoms duration can be offset by the rate of adverse events particularly when no benefits were seen in the rate of admission or serious adverse events. On a societal level, there may not be sufficient justification for the cost of stockpiling Oseltamivir.

The FDA only allows claims of efficacy of Oseltamivir for the prevention and treatment of influenza symptoms and not for other outcomes. The FDA classifies the overall performance of Oseltamivir as “modest”.

The 2016-17 CDC guidance for the use of antivirals (WEB LINK) strongly recommends antiviral therapy for those requiring hospital admission and those at high risk for complications of influenza. The CDC consider all children less than 5 and particularly those less than two years of age at high risk. Infants less than 6 months of age have the highest rates hospitalization and death.

The CDC states that “antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset.”

SEE ALSO:

COCHRANE REVIEW (Includes both Oseltamivri and Zanamivir)
Tom Jefferson, Mark A Jones , Peter Doshi , Chris B Del Mar , Rokuro Hama , Matthew J Thompson , Elizabeth A Spencer , Igho J Onakpoya , Kamal R Mahtani , David Nunan , Jeremy Howick, Carl J Heneghan for the Cochrane Acute Respiratory Infections Group
Neuraminidase Inhibitors for Preventing and Treating Influenza in Adults and Children
Cochrane Systematic Review: April 10, 2014, PubMed ID: 24718923
WEB LINKS: Summary PDF (5 pages), Standard PDF (283 pages), Full PDF (560 pages)

Heneghan CJ, Onakpoya I, Thompson M, Spencer EA, Jones M, Jefferson T.
Zanamivir for Influenza in Adults and Children: Systematic Review of Clinical Study Reports and Summary of Regulatory Comments.
BMJ. 2014 Apr 9;348:g 2547, PubMed ID: 24811412

NEUROLOGY

1. Bell's Palsy: Prednisone and/or Acyclovir: NEJM 2007
2. Febrile Seizure: Acetaminophen & Recurrence: Ped 2018
3. Encephalitis: Acyclovir Timing: Pediatrics 2011
4. Meningitis: Meningitis Score Derivation: Pediatrics 2002
5. Meningitis: Meningitis Score Validation: JAMA 2007
6. Meningitis: BMS Meta-Analysis: Arch Dis Child. 2012
7. Migraine Headache: ED Therapy: Pediatrics 2015
8. Migraine Headache: Low Dose Propofol: J EM 2017
9. Migraine Headache: Therapy Meta-Analysis: BMJ 2004
10. Status Epilepticus: Benzo Meta-Analysis: Acad EM 2010
11. Status Epilepticus: Diazepam vs Lorazepam: JAMA 2014
12. Status Epi: Keppra vs Phenytoin (PERUKI) Lancet 2019
13. Status Epi: Keppra vs Phenytoin (PREDICT Lancet 2019
14. Status Epilepticus: Prehospital Benzo: NEJM 2012
15. VP Shunt Obstruction: Rapid MRI: Pediatrics 2014

BELL'S PALSY:
PREDNISONE AND/OR ACYCLOVIR

In patients > 16 years of age with peripheral facial nerve (Bell's) palsy, does Acyclovir and Prednisone when used individually or in combination within 72 hours of symptom onset when compared to Placebo improve facial nerve function at 3 and 9 months?

Lili Banan, M.D., Michael Mojica, M.D.
October 2008

Sullivan FM, Swan IR, Donnan PT, Morrison JM, Smith BH, McKinstry B, Davenport RJ, Vale LD, Clarkson JE, Hammersley V, Hayavi S, McAteer A, Stewart K, Daly F.

EARLY TREATMENT WITH PREDNISONE OR ACYCLOVIR IN BELL'S PALSY.

N Engl J Med. 2007 Oct 18;357(16):1598-607.
PubMed ID: 17942873

STUDY DEFINITIONS	
POPULATION	Inclusion: Unilateral facial-nerve weakness of no identifiable cause, presented to primary care or the emergency department, referred to otorhinolaryngologist within 72 hours of symptom onset. Exclusion: Pregnancy, breast-feeding, uncontrolled diabetes (glycated hemoglobin level, >8%), peptic ulcer disease, suppurative otitis media, herpes zoster, multiple sclerosis, systemic infection, sarcoidosis Setting: Multicenter (referral from primary care, ED, dentists), enrollment 6/2004-6/2005, follow up until 3/2007
INTERVENTION GROUPS (4)	1. Prednisone 25 mg BID x 10 days AND Placebo x 10 days 2. Acyclovir 400 mg 5 times a day x 10 days AND Placebo x 10 days 3. Prednisone 25 mg BID AND Acyclovir 400 mg 5 times a day x 10 days 4. Placebo x 10 days AND Placebo x 10 days
OUTCOME	Primary Outcome: House–Brackmann scale (see Appendix) at 3 months (Seen at 9 months if incomplete recovery at 3 months) Complete recovery defined as Grade 1 Incomplete recovery defined as Grade ≥ 2 Assessed by facial appearance in digital photos (at rest, with a forced smile, with raised eyebrows, and with eyes tightly closed). Panel of three experts: Otorhinolaryngologist, neurologist, plastic surgeon Secondary Outcomes: Only obtained in patients without recovery at 3 months Health-related quality of life (Health Utilities Index Mark 3) Facial appearance (Derriford Appearance Scale 59) Pain (Brief Pain Inventory). Adverse events Compliance: First visit, by phone on day 7, within a week after the final day of the study. Patients were instructed to return pill containers and any unused capsules
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were assigned to each group by an independent, automated phone system. Patients were first randomized to Acyclovir or Placebo and then randomized to receive Prednisone or Placebo.
Was randomization concealed?	Yes. Allocation was concealed. The randomization technique did not allows for assignment bias.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Table 1. The Prednisone group had slight fewer people identified in the 1st 24 hours. Later onset of therapy could possibly lead to a bias against Prednisone
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Each patient received two bottles of odorless capsules with an identical appearance. Patients, investigators and outcome assessors were unaware of treatment allocation.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. 10% (55/551) patients were lost to follow-up, either by elimination from the study, unable to be reached, or by death.
Were patients analyzed in the groups to which they were randomized?	Yes. All subjects were analyzed in their assigned groups. (Intention to treat analysis).
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 496
Referral: 88.9% from primary care
Mean age: 44 years
Mean degree of facial paralysis: Moderate-Severe
Time to treatment: 54% (<24 hours), 86% (<48 hours)
Compliance: 90%
Recovery: 72% within 3 months

Study groups analyzed as:
Prednisone YES: Prednisone/Placebo and Prednisone/Acyclovir groups
Prednisone NO: Acyclovir/Placebo and Placebo/Placebo groups
Acyclovir YES: Acyclovir/Placebo and Prednisone/Acyclovir groups
Acyclovir NO: Prednisone/Placebo and Prednisone/Placebo groups

Primary Outcome:
House-Brachmann Scale of Facial Nerve Function (Grade 1: Normal Function)

PREDNISONE	3 MONTHS	9 MONTHS
Prednisone	83.0%	94.4%
No Prednisone	63.6%	81.6%
Risk Difference (Unadjusted)	19.4% (11.6, 26.9%)	12.8% (7.2, 18.6%)
Adjusted Odds Ratio (P/No P)	2.44 (1.55, 3.84)	3.32 (1.72, 6.44)

ACYCLOVIR	3 MONTHS	9 MONTHS
Acyclovir	71.2%	85.4%
No Acyclovir	75.7%	90.8%
Risk Difference (Unadjusted)	4.5% (-3.3, 12.3%)	5.3% (-0.4, 11.1%)
Adjusted Odds Ratio (A/No A)	0.85 (0.55, 1.34)	0.61 (0.44, 1.11)

Secondary Outcomes: No significance differences in:
Health Utilities Index Score
Brief Pain Inventory Score
Deriford Appearance Score

Adverse Events:
There were no serious adverse events.
3 deaths during the trial were not deemed related

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?
The 95% confidence interval in the tables above indicate the precision and the statistical significance of each comparison. The confidence interval for the adjusted odds ratio and unadjusted risk difference for Prednisone compared to No Prednisone indicates a statistically significant difference at 3 months and at 9 months. The confidence interval for the adjusted odds ratio and unadjusted risk difference for Acyclovir compared to No Acyclovir does not indicate a statistically significant difference. A difference in the complete-recovery rate of at least 10 to 12 percentage points was considered to be clinically significant by the authors in the sample size determination. Therefore, the Prednisone comparison (19.4% at 3 months, 12.8% at 6 months) is considered clinically significant by the authors. The Acyclovir comparison (4.5% at 3 months, 5.3% at 6 months) is not considered clinically significant by the authors.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	No. The mean age was 44 years, much older than our pediatric population though it is unclear if this would make a difference. It is also unclear if the Scottish patients in this study who were referred to ENT are similar to the population presenting to a US ED or represent referral bias. Finally, the efficacy of therapy should be considered in the context of the epidemiology of the disease. We do not know the incidence of HSV related Bell's Palsy in the study population.
Were all patient important outcomes considered?	Yes. They were very thorough and measured function on 3 scales.
Are the likely treatment benefits worth the potential harm and costs?	Yes. For Prednisone, the benefits of a short course of therapy are clear. It improves the outcome substantially. The number needed to treat (NNT) at 3 months to achieve 1 additional complete recovery is: NNT = 1/ARD = 1/0.194 = 5. At 9 months the NNT = 1/ARD = 1/0.128 = 8. There was not a benefit for Acyclovir either alone or in combination with Prednisolone

CLINICAL BOTTOM LINE

BACKGROUND: Studies have demonstrated that Prednisone and Acyclovir could be useful in treating Bell's Palsy. Traditionally, both have been used to some degree. Prednisone is thought to reduce facial nerve edema. Acyclovir is thought to directly treat HSV infection.

CLINICAL QUESTION: In patients >16 years of age with peripheral facial nerve (Bell's palsy) does Acyclovir and Prednisone when used individually or in combination when compared to Placebo within 72 hours of onset improve facial nerve function at 3 and 9 months?

DESIGN/VALIDITY: This was a well-designed randomized clinical trail comparing 4 groups (Prednisone/ Placebo. Acyclovir/Placebo, Prednisone/Acyclovir and Placebo/Placebo). It included 496 patients in the primary intention to treat analysis. The only major validity concern is that there was no assessment for the presence of HSV infection. If none of the patients had HSV infection it would not be surprising if there was no benefit to Acyclovir. Patients with herpes zoster were excluded.

PRIMARY RESULTS: In the intention to treat analysis there was a higher proportion of patients with normal facial nerve function (House–Brackmann scale Grade 1) in those who received Prednisone than in those who did not receive Prednisone at 3 months (Prednisone: 83.0%, No Prednisone: 63.6%, Absolute risk difference: 19.4%, 95% CI (11.6, 26.9%)), and at 9 months (Prednisone: 94.4%, No Prednisone: 81.6%, Absolute risk difference: 12.8%, 95% CI (7.2, 18.6%)).
There was no statistically significant difference in the primary outcome at 3 or 9 months for those receiving Acyclovir either alone or in combination with Prednisone. There were no significant adverse events attributed to the study medications.

APPLICABILITY: The applicability to US pediatric populations is unclear but there is no specific reason to believe that the study results would not be generalizable to those meeting the study inclusion and exclusion criteria. The generalizability to treatment with Prednisone after 72 hours is also not clear.

AUTHOR'S CONCLUSION: "In conclusion, we have provided evidence that the early use of oral prednisolone in patients with Bell's palsy is an effective treatment. The mechanism of action may involve modulation of the immune response to the causative agent or direct reduction of edema around the facial nerve within the facial canal. Treatment with unesterified acyclovir at doses used in other trials either alone or with corticosteroids had no effect on the outcome. Therefore, we cannot recommend acyclovir for use in the treatment of Bell's palsy. A recent study in Japan suggested that Valacyclovir (a prodrug that achieves a level of bioavailability that is three to five times that of acyclovir) may be a useful addition to prednisolone. However, the Japanese study was smaller than ours, patients were treated in tertiary centers, and the outcome assessors were aware of the study-group assignments; therefore, the results of that study should be interpreted with caution."

POTENTIAL IMPACT: This study supports the use of Prednisone in patients with peripheral facial nerve (Bell's) palsy within 3 days of symptom onset. In the absence of clinical signs of HSV infection, there does not appear to be a benefit of empiric Acyclovir though evidence of HSV infection was not assessed in the study population.

APPENDIX: HOUSE-BRACKMANN GRADING

HOUSE-BRACKMANN FACIAL NERVE GRADING SYSTEM
GRADE I: NORMAL
Normal facial function in all areas
GRADE II: SLIGHT DYSFUNCTION
Gross: slight weakness noticeable on close inspection; may have very slight synkinesis
At rest: normal symmetry and tone
Motion: forehead: moderate to good function; eye: complete closure with minimum effort; mouth: slight asymmetry.
GRADE III: MODERATE DYSFUNCTION
Gross: obvious but not disfiguring difference between two sides; noticeable but not severe synkinesis, contracture, and/or hemi-facial spasm.
At rest: normal symmetry and tone
Motion: forehead: slight to moderate movement; eye: complete closure with effort; mouth: slightly weak with maximum effort.
GRADE IV: MODERATE SEVERE DYSFUNCTION
Gross: obvious weakness and/or disfiguring asymmetry
At rest: normal symmetry and tone
Motion: forehead: none; eye: incomplete closure; mouth: asymmetric with maximum effort.
GRADE V: SEVERE DYSFUNCTION
Gross: only barely perceptible motion
At rest: asymmetry
Motion: forehead: none; eye: incomplete closure; mouth: slight movement
GRADE VI: TOTAL PARALYSIS
No movement

House, J.W., Brackmann, D.E.
Facial Nerve Grading System.
Otolaryngol. Head Neck Surg, [93] 146–147. 1985. PubMed ID: 3921901

FEBRILE SEIZURE:
ACETAMINOPHEN FOR RECURRENCE

In children 6-60 months of age presenting to the emergency department with a febrile seizure does Acetaminophen administered rectally every 6 hours if febrile until 24 hours after the initial seizure when compared to not receiving an antipyretic, decrease the rate of seizure recurrence during the same febrile illness?

Michael Mojica, MD

December 2018

Murata S, Okasora K, Tanabe T, Ogino M, Yamazaki S, Oba C, Syabana K, Nomura S, Shirasu A, Inoue K, Kashiwagi M, Tamai H.

ACETAMINOPHEN AND FEBRILE SEIZURE RECURRENCES DURING THE SAME FEVER EPISODE.

Pediatrics. 2018 Nov;142(5). pii: e20181009.
PubMed ID: 30297499

STUDY DEFINITIONS	
POPULATION	Inclusion: 6-60 months, febrile seizure (seizure with temperature ≥ 38 C without a central nervous system infection). Stratified by age (6-21 and 22-60 months) Exclusion: ≥ 2 prior febrile seizures during the current febrile illness, febrile status epilepticus (≥ 15 minutes), epilepsy, chromosomal abnormalities, inborn errors of metabolism, brain tumor, intracranial hemorrhage, hydrocephalus, history of intracranial surgery, diarrhea, use of antihistamines. Administered diazepam suppository prior to arrival and parents requesting diazepam. Setting: Single Emergency Department (Japan), 5/2015-4/2017
INTERVENTION	Acetaminophen group: 10 mg/kg rectally for fever > 38.0C. 1st dose in emergency department then Q6H until 24 hours after initial seizure
CONTROL	No antipyretics group: Instructed not to give any antipyretics for 24 hours after initial seizure
OUTCOME	Febrile seizure recurrence
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were allocated to treatment groups based on a random-number table.
Was randomization concealed?	Unclear. It was not explicitly stated that there was no possibility patients were not allocated to the groups they were randomized to.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Patients were similar with regard to seizure, demographic and laboratory data (Table 1). This was also true when stratified by age group (6-21 months and 22-60 months). A logistic regression analysis was conducted using variables associated with recurrence in the bivariable analysis.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study was not blinded. However, the outcome febrile seizure recurrence is fairly objective and unlikely to be biased based on knowledge of the study group.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Of the 443 patients (prior to exclusion for non-adherence to the study regimen) only 5 (1.1%) were lost to follow up).
Were patients analyzed in the groups to which they were randomized?	No. This was a per protocol analysis as patients that were non-compliant with study instruction were not included in the analysis. However, only 2.3% (10/428) were non-adherent to the study interventions so that it is unlikely that an intention to treat analysis would be markedly different.
Was the trial stopped early?	No. The trial was not stopped early. The authors estimated 400 patients were required for a logistic regression analysis with 5 independent variables. 428 patients were included in the primary per protocol analysis.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 428
Acetaminophen group: 219 (10 excluded due to non-compliance (7) and lost to follow up (3))
No Antipyretic group: 209 (5 excluded due to non-compliance (3) and lost to follow up (2))

FEBRILE SEIZURE RECURRENCE: ALL PATIENTS AND STRATIFIED BY AGE			
	6-60 months	6-21 months	22-60 months
Acetaminophen Group	9.1% (20/219)	13.2% (16/121)	4.1% (4/98)
No Antipyretic Group	23.5% (48/204)	24.3% (27/11)	22.6% (21/93)
Risk Difference (95% CI)	14.4% (7.4, 21.4%)	11.1% (1.0, 21.1%)	18.5% (9.1, 28.3%)
Relative Risk (95% CI)	0.38 (0.23, 0.63)	0.54 (0.31, 0.95)	0.18 (0.09, 0.28)
Overall Recurrence: 68/423 (16%)			

Bivariable Analysis: Older age, longer duration of seizure and acetaminophen were associated with a decreased recurrence of seizures. The following variables were not significant predictors in the bivariable analysis: sex, past history and familial history of febrile seizures, the time interval between fever and febrile seizure and the temperature on ED arrival

LOGISTIC REGRESSION (TABLE 2)	
INDEPENDENT PREDICTOR	ADJUSTED ODDS RATIO (95% CI)
Acetaminophen (No Antipyretic/Acetaminophen)	5.6 (2.3, 13.3)
Age (1-month decrements)*	1.08 (1.03, 1.11)
Seizure duration (1-minute decrements)*	1.15 (0.99, 1.32)
*Recurrence rate increased as age and seizure duration decreased	

Adverse Events: No hypotension, hypothermia or anaphylaxis

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence intervals for the risk differences and relative risks and well as the adjusted odds ratios are presented above. The confidence intervals for most analyses are fairly wide.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Unclear. Japanese patients have a higher risk of febrile seizures (7-11%) compared to the US (2-5%). It is unclear if the rate of recurrence differs.
Were all patient important outcomes considered?	Yes. Recurrence of febrile seizure would be the outcome of most interest to parents (aside from long term risk of epilepsy). There were no adverse events reported in the Acetaminophen group.
Are the likely treatment benefits worth the potential harm and costs?	In addition to decreasing febrile seizure recurrence, an antipyretic has the added benefit of symptomatic relief and decreasing insensible losses. For every 7 patients treated with Acetaminophen, 1 additional patient did not have a febrile seizure recurrence. NUMBER NEED TO TREAT Age Category — Risk Difference — NNT 6-60 months — 14.4% (7.4, 21.4%) — 7, 95% CI (5, 13) 6-21 months — 11.1% (1.0, 21.1%) — 9, 95% CI (5, 95) 22-60 months — 18.5% (9.1, 28.3%) — 5, 95% CI (4, 11)

CLINICAL BOTTOM LINE

BACKGROUND: Febrile seizures are the most common type of seizure in children. Although benign, they are very frightening to parents. Most evidence suggests that antipyretics do not reduce the risk of recurrence. In a study of 104 patients with simple febrile seizure, there was no difference in recurrence in the standing acetaminophen group (7.5%) when compared to sporadic acetaminophen use (7.8%) (Schnaiderman, Eur J Pediatr. 1993, PubMed ID: 8223808). A meta-analysis including 3 randomized clinical trials with 540 children who had a history of prior febrile seizures found no difference in the rate of seizure recurrence during subsequent febrile episodes when comparing standing antipyretic (Acetaminophen, Ibuprofen or Diclofenac)(22.7%) to Placebo (22.7%) (OR 0.9, 95% CI: 0.57-1.43) (Rosenbloom, Eur J Pediatr Neurol 2013, PubMed ID: 23702315). Despite the lack of evidence, some pediatricians recommend a standing dose of antipyretics to parents with some suggesting alternating between Ibuprofen and Acetaminophen.

CLINICAL QUESTION: In children 6-60 months of age presenting to the emergency department with a febrile seizure does Acetaminophen administered rectally every 6 hours if febrile until 24 hours after the initial seizure when compared to not receiving an antipyretic, decrease the rate of seizure recurrence during the same febrile illness?

DESIGN/VALIDITY: This was a randomized clinical trial of children presenting to the emergency department with a febrile seizure. Patients were randomized to rectally administered Acetaminophen (10 mg/kg) every 6 hours for a temperature greater than 38C in the first 24 hours after seizure onset or no antipyretics. It is surprising that an IRB would approve a study arm that did not included an antipyretic that could improve patients symptomatically. The study was not blinded though the primary outcome of seizure recurrence is fairly objective. A subgroup analysis based on the distinction between simple and complex febrile seizure would have been helpful.

PRIMARY RESULTS: The study included 428 patients (Acetaminophen group: 219, No Antipyretic group: 209). There was a statistically significant reduction in febrile seizure recurrence during the same febrile episode in the Acetaminophen group when including all patients (14% (7.4, 21.4%)) as well as when stratified by age (6-21 months: 11.1%, 95% (1.0, 21.1%), 22-60 months: 18.5%, 95% CI (9.1, 28.3%)). In the logistic regression analysis, 3 variables were found to be independent predictors of febrile seizure recurrence (younger age, shorter duration of seizure and no antipyretic use). The no antipyretic group had an adjusted odds ratio of 5.6, 95% CI (2.3, 13.3). The following variables were not significant predictors in the bivariable analysis: sex, past history and family history of febrile seizures, the time interval between fever and febrile seizure and the temperature on ED arrival. It is interesting that the decrease in seizure recurrence was seen at a lower dose (10 mg/kg) and an and at a longer interval (Q6H) then is typically used in the U.S.

FEBRILE SEIZURE RECURRENCE: ALL PATIENTS AND STRATIFIED BY AGE			
	6-60 months	6-21 months	22-60 months
Acetaminophen Group	9.1% (20/219)	13.2% (16/121)	4.1% (4/98)
No Antipyretic Group	23.5% (48/204)	24.3% (27/11)	22.6% (21/93)
Risk Difference (95% CI)	14.4% (7.4, 21.4%)	11.1% (1.0, 21.1%)	18.5% (9.1, 28.3%)
Relative Risk (95% CI)	0.38 (0.23, 0.63)	0.54 (0.31, 0.95)	0.18 (0.09, 0.28)
Overall Recurrence: 68/423 (16%)			

LOGISTIC REGRESSION (TABLE 2)	
INDEPENDENT PREDICTOR	ADJUSTED ODDS RATIO (95% CI)
Acetaminophen (No Antipyretic/Acetaminophen)	5.6 (2.3, 13.3)
Age (1-month decrements)*	1.08 (1.03, 1.11)
Seizure duration (1-minute decrements)*	1.15 (0.99, 1.32)
*Recurrence rate increased as age and seizure duration decreased	

APPLICABILITY: The study was conducted in a single Emergency Department in Japan where there is a higher rate of febrile seizures. In is unclear, if these results can be generalized to those meeting the study's inclusion and exclusion criteria in other countries and care settings. In addition, the study had a high rate of recurrence in the non-antipyretic group (23.5%). The authors based their analysis on a presumed recurrence rate of 15%. The number needed to treat is 7. For every 7 patients treated with Acetaminophen, 1 additional patient did not have a febrile seizure recurrence.

AUTHOR'S CONCLUSION: "Acetaminophen may reduce the recurrence of febrile seizures during the same fever episode and thus can be considered safe for use in children with febrile seizures. Nevertheless, the constant use of acetaminophen in children with febrile seizures is not recommended because the outcome of febrile seizures is usually favorable. The most important aspect of clinical practice against febrile seizures is providing appropriate explanations to parents to relieve anxiety and to ensure appropriate use of acetaminophen on the basis of the individual conditions."

POTENTIAL IMPACT: It is unclear how this study's conclusion fit into the existing literature that has not found a benefit to antipyretics on febrile seizure recurrence. There are some applicability issues that may not allow us to generalize to U.S. treatment centers. However, the number needed to treat was very low (NNT = 7) and no adverse events were reported. It seems prudent to treat the child's fever for symptomatic relief with the potential added benefit of a decrease in seizure recurrence. How to do this without adding to parental anxiety is unclear.

HSV ENCEPHALITIS: ACYCLOVIR TIMING

In neonates ≤ 28 days old with a herpes simplex virus infection, does delayed Acyclovir therapy (> 24 hours) as compared to early Acyclovir therapy (< 24 hours) increase the odds of in-hospital death?

Janienne Kondrich, M.D., Michael Mojica, M.D.
February 2012

Shah SS, Aronson PL, Mohamad Z, Lorch SA.

DELAYED ACYCLOVIR THERAPY AND DEATH AMONG NEONATES WITH HERPES SIMPLEX VIRUS INFECTION.

Pediatrics. 2011 Dec;128(6):1153-60.
PubMed ID: 22123868

STUDY DEFINITIONS	
POPULATION	Inclusion: Diagnosis of HSV (ICD-9 Codes) and received intravenous Acyclovir Subgroups: HSV isolated to skin, eyes, mouth vs complications meningitis/sepsis Exclusion: Received intravenous Acyclovir treatment > 7 days after admission Setting: National Children's Hospital Database (n=41). 1/2003-12/2009
EXPOSURE	Early Acyclovir: First day of hospitalization
CONTROL	Delayed Acyclovir: After 1 day and before 7 days after admission.
OUTCOME	Primary Outcome: Death before hospital discharge
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
Aside from the exposure of interest did the exposed and control groups start and finish with the same risk for the outcome?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or did statistical adjustments address the imbalance).	Yes. However, the early Acyclovir group had a greater proportion of patients who received anticonvulsants, suggesting these patients were sicker at the time of presentation. This would bias the results against early Acyclovir therapy. The early Acyclovir group also had more patients who underwent skin testing for herpes simplex virus, which would be expected.
Were the circumstances and methods for detecting the outcome similar?	Yes. In cohort studies, we must be careful of surveillance bias, the tendency to look more carefully for an outcome in one of the comparison groups. The outcome in this study – death upon discharge from the hospital – is unequivocal, and not susceptible to this form of bias.
Was follow-up sufficiently complete?	Yes. The outcome of all patients is known at the time of hospital discharge.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

1086 neonates with HSV infection (mean age 10 days)
17.7% HSV with complications
24.1% with delayed Acyclovir (86% on days 2 or 3)

Univariate Analysis

Risk Death (Delayed Acyclovir) = 25/262 = 9.5%
Risk Death (Early Acyclovir) = 54/824 = 6.6%
Absolute Risk Difference: 9.5 – 6.6% = 2.9%, 95% CI (-0.6, 7.4%)
Relative Risk (Late/Early) = (9.5%)/(6.6%) = 1.4, 95% CI (0.92, 2.92)
Odds Ratio (Late/Early) = 1.5, 95% CI (0.92, 2.47)

In the univariate analysis, delayed Acyclovir therapy was not associated with a statistically or clinically significant increase in the risk or odds of death.
Risk of deaths were highest in those < 7 days old

Multivariate Analysis:

Odds Ratio = 2.62, 95% CI (1.34, 5.09)

In the multivariate analysis, delayed Acyclovir therapy was associated with a greater than 2.6-fold increase in the odds of death.

There was a “dose-response” relationship: Death increased with each additional day of delay. Mortality: Day 1: 6.6%, Day 2: 8.3%, Day 3: 8.8%, Day 4-7: 16.7%

HOW PRECISE IS THE ESTIMATE OF THE RISK?

Confidence intervals as above. The confidence interval for the OR in the univariate analysis was neither clinically not statistically significant. The confidence interval for the adjusted odds ratio is statistically significant and clinically significant (based on the authors definition of clinically significant if the odds ratio is > 1.8)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	The patients in the study group had a higher percentage of neonates with identified congenital anomalies (13.1% overall) than in the population of infants we see. Unfortunately, because this was an observational study, it is unclear what patient characteristic determined testing for HSV or the time of administration of Acyclovir.
Was follow-up sufficiently long?	The primary outcome was death during the hospital admission. All patient data was available during the length of admission. Follow up after discharge was not performed.
Is the exposure similar to what might occur in my patient?	The exposure in the study is the time to administration of Acyclovir. Patients without a history or examination findings consistent with HSV and with no-specific CSF findings may have a delay in treatment of occult HSV infection.
What is the magnitude of the risk?	The odds ratio for the regression analysis indicated a 2.62 odds of mortality in those receiving Acyclovir after 24 hours.
Are there any benefits that offset the risks associated with exposure?	The exposure in this study is the time to administration of Acyclovir. The benefits far exceed the risks in those with HSV encephalitis. Treating those without HSV meningitis would expose them to the adverse effects of Acyclovir without any benefits.

CLINICAL BOTTOM LINE

BACKGROUND: HSV infection in neonates is classified in three ways: a localized infection of the skin, eyes and/or mouth, CNS infection, and disseminated disease: HSV is a significant cause of morbidity and mortality in this age group. Despite the severity of disease in those infected, there remains a subset of patients for whom HSV testing is performed who do not receive Acyclovir therapy at the time of hospital admission. Prior research has suggested that clinical outcomes from HSV infection could be improved if this treatment delays were eliminated.

CLINICAL QUESTION: In neonates ≤ 28 days old with a herpes simplex virus infection, does delayed Acyclovir therapy (> 24 hours) as compared to early Acyclovir therapy (<24 hours) increase the odds of in hospital death?

DESIGN/RISK OF BIAS: This was a multicenter observational cohort study that looked for an association between timing of Acyclovir administration and survival at time of hospital discharge. The study included 1,007 patients with HSV of which 79 (7.8%) died. Multiple analysis techniques were used to account for biases inherent to retrospective observational studies including propensity scoring and analysis for subgroups such as HSV without complications and analysis of delay in Acyclovir due to transfer.

PRIMARY RESULTS: The study found a 2.6 folds increase in odds of death in the group who received the first dose of Acyclovir greater than one day after admission when compared to those receiving it on day one. There were several potential sources of bias in this study, most of which would have swayed the results toward finding no difference between the groups. This suggests that the difference in survival between the early and late Acyclovir treatment groups is perhaps even greater than this study found. The number needed to harm calculated from the odds ratio indicates that for every 11 patients treated with Acyclovir after day 1 of admission there would be 1 addition death during admission when compared to those who received Acyclovir on day 1.

APPLICABILITY: The use or a large multi Children's hospital database likely makes this study's result applicable to most patient populations though referral bias should be considered.

AUTHOR'S CONCLUSION: "This multicenter observational study found that delayed initiation of Acyclovir therapy was associated with in-hospital death among neonates with HSV infection. Our data support the use of empiric Acyclovir therapy for neo-nates undergoing testing for HSV infection."

POTENTIAL IMPACT: This was a well-conducted study that supports empiric Acyclovir treatment for neonates on whom HSV testing is sent. It did not, however, explore the important question of which patients should be tested for HSV on initial presentation. Further study is required to determine if HSV testing should be part of the routine evaluation of febrile newborns, or if high-risk and low-risk patient groups can be reliably identified with based on clinical and laboratory parameters.

MENINGITIS:
BACTERIAL MENINGITIS SCORE DERIVATION

In children aged 29 days to 19 years admitted to a single urban children's hospital with a diagnosis of meningitis, are there objective and readily available parameters to distinguish bacterial from aseptic meningitis and identify a very low-risk group who may be suitable for outpatient management?

Joshua Beiner, M.D., Michael Mojica, M.D.

February 2, 2016

Nigrovic LE, Kuppermann N, Malley R.

DEVELOPMENT AND VALIDATION OF A MULTIVARIABLE PREDICTIVE MODEL TO DISTINGUISH BACTERIAL FROM ASEPTIC MENINGITIS IN CHILDREN IN THE POST-HAEMOPHILUS INFLUENZAE ERA

Pediatrics. 2002 Oct;110(4):712-9.
PubMed ID: 12359784

STUDY DEFINITIONS	
POPULATION	Inclusion: 29 days – 19 years, ICD9 final diagnosis of meningitis, Exclusion: 1. Antibiotics within prior 72 hours of lumbar puncture and blood culture 2. Neurosurgical procedure 3. Sepsis 4. Immunocompromised 5. Other focal bacterial infection requiring admission Setting: Single Children's Hospital, 9/1992-6/2000
RULE PARAMETERS	Rule parameters: Season, history, physical examination and laboratory parameters Those available in time to inform emergency department disposition
REFERENCE STANDARD	Bacterial Meningitis: (+) CSF Culture or (+) CSF pleocytosis (> 7 WBC/mm^3) and [(+) Blood culture or (+) CSF latex agglutination] Aseptic Meningitis: (-) CSF culture and (-) Blood culture and (-) CSF latex agglutination
OUTCOME	Decision rule characteristics
DESIGN	Observational: Retrospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. Authors searched prior studies and 2 previously published multivariate models for candidate parameters. Objective parameters which were biologically plausible, that previously demonstrated capability of distinguishing bacterial from aseptic meningitis, and which would be readily available at the time of evaluation were included. Consequently, certain measures with proven predictive power like CSF TNF-α and IL-6 were intentionally excluded. Further, measures of illness severity, which might be subjective, were also excluded.
Were all important predictors present in significant proportion of the study population?	Yes, for the dichotomous predictors. A small but non-nominal proportion of patients in the derivation and validation groups presented with seizures (6.7%) or had a positive gram strain (13.1%). We cannot determine whether a significant proportion of patients with continuously measures predictors were included because only the means and standard deviations were reported. 96% of the sample had data available to complete the Bacterial Meningitis Score (BMS).
Were the outcome event and predictors clearly defined?	Yes. The main outcome was the accuracy of the BMS when applied to the validation set. Predictors significantly capable of distinguishing bacterial from aseptic meningitis were identified in the univariate analysis. Those with independent discriminatory ability were identified from the multivariate logistic regression analysis and entered in the recursive partitioning analysis. These predictors then formed the decision tree using recursive partitioning.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Unlikely. The BMS was formulated and scored in a retrospective manner. Those who did the data extraction may have helped determine the main outcome measure. However, both the predictors and the outcomes are objective, with the possible exception of the “seizure” predictor, and should not be biased by lack of blinding.
Was the sample size adequate (including an adequate number of outcome events)?	Sample size determination was not included due to the nature of the study. Overall, it was a large sample of patients with meningitis from a single center that is a regional referral center. Also, the prevalence of bacterial meningitis in the study cohort (18%) was higher than population estimates. There were greater than 10 cases of bacterial meningitis per predictor, a general rule of thumb for assessing adequacy of outcome events when using logistic regression analyses.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

DERIVATION COHORT

	BACTERIAL MENINGITIS		
	YES	NO	
HIGH RISK (BMS ≥ 1)	80	105	185
LOW RISK (BMS = 0)	2	250	252
	82	255	437

Prevalence: 82/437 = 18.8%
Sensitivity: 80/82 = 97.6%, 95% CI (91.5, 99.3%)
Specificity: 250/255 = 70.4%, 95% CI (65.5, 74.9%)
Predictive Value (-) Rule: 250/272 = 99.2%, 95% CI (97.2, 99.8%)
Predictive Value (+) Rule: 80/185 = 43.2%, 95% CI (36.3, 50.4%)
Likelihood Ratio (+) Rule: (80/82)/(105/255) = 3.3, 95% CI (2.8 – 3.9)
Likelihood Ratio (-) Rule: (2/82)/(250/255) = 0.035, 95% CI (0.01 – 1.4)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

58% (252/437) of patients were low risk (i.e., BMS = 0) in the derivation group. This group could potentially be managed as outpatients, either with or without receipt of antibiotics

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

Yes, 1/3 of the sample functioned as the internal validation group. Rule characteristics are similar

VALIDATION (INTERNAL) COHORT

	BACTERIAL MENINGITIS		
	YES	NO	
HIGH RISK (BMS ≥ 1)	38	52	90
LOW RISK (BMS = 0)	0	144	144
	38	196	234

Prevalence: 38/234 = 16.2%
Sensitivity: 38/38 = 100%, 95% CI (90.8, 100%)
Specificity: 144/196 = 73.5%, 95% CI (66.9, 79.2%)
Predictive Value (-) Rule: 144/144 = 100%, 95% CI (97.4, 100%)
Predictive Value (+) Rule: 38/90 = 42.2%, 95% CI (32.5, 52.5%)
Likelihood Ratio (+) Rule: (38/38)/(52/196) = 3.77, 95% CI (2.99, 4.76)
Likelihood Ratio (-) Rule: (0/38)/(144/196) = Undefined (0 in numerator)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see appendix)	☐ I ☐ II ☐ III ■ IV Level IV rules have been derived only or validated only in split samples, large retrospective databases or by statistical methods. Level IV rules require further validation before they can be applied clinically
Does the rule make clinical sense?	Yes. The rule satisfies its objective of being biologically plausible, available at the time of evaluation, and objective, with the possible exception of the “seizure activity” predictor. It also has the ability to significantly reduce inpatient resources.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Yes. 4 of the 5 predictors are objective. Seizure activity prior to arrival has the potential for subjectivity, but given the retrospective nature of the study there is no way to perform that analysis for this predictor.
Is the rule applicable to the patients in my practice?	Yes. The setting is a children’s hospital that is a regional referral center. The prevalence of bacterial meningitis was higher than other published population estimates. Given that the pre-test probability of bacterial meningitis might be significantly lower at out institution, it would be more appropriate to use the likelihood ratios established in the study to generate patient specific post-test probability rather than the published predictive values, which are affected by prevalence of disease.
Will the rule results change my management strategy?	Unclear. The answer to this question is dependent on your existing management strategy. This rule requires broad validation before it can be used clinically.
What are the benefits of applying the rule to my patients?	The BMS is simple to use to discriminate those at very high or low risk for bacterial meningitis. 60% of the sample were classified as very low risk with a BMS of 0. A significant portion of this group could be managed as an outpatient, either with or without antibiotic coverage. A BMS of ≥ 2 had high positive predictive value and sensitivity for bacterial meningitis and might allow for more rapid risk stratification and resource allocation to such patients.
What are the risks of applying the rule to my patients?	2/404 (0.5%) of patients with a BMS of 0 had bacterial meningitis and might have been discharged. 1 of the 2 misclassified patients were pre-treated with antibiotics prior to LP. The article does not mention why this patient was not excluded as having pre-treatment. Perhaps the pre-treatment was greater than 72 hours before LP. The upper limit of the 95% CI suggests that the missed rate can reach 1.8% due to the relative small sample size.

CLINICAL BOTTOM LINE

BACKGROUND: Despite highly effective vaccination programs, there are still approximately 6,000 new cases of bacterial meningitis annually, half of which are in the pediatric population. Bacterial meningitis has a considerable mortality rate, between 3-12% for the most common etiologies, and even higher rates of neurologic sequelae. At the time of patient presentation, distinguishing between bacterial and aseptic meningitis is often difficult, and patients often get admitted to the hospital for empiric antibiotics pending culture results. Many individual laboratory tests lack the necessary sensitivity or specificity to distinguish bacterial from aseptic meningitis while others are not readily available during initial patient evaluation when results could impact clinical decision making. Previous attempts at risk-stratification have had predictive power, but were established prior to widespread use of the HIB conjugate vaccination or were not validated. The authors sought to develop and validate a predictive model available at the time of patient evaluation to distinguish bacterial from aseptic meningitis, and in the process, identify a subset of patients who might be candidates for outpatient management.

CLINICAL QUESTION: In children aged 29 days to 19 years admitted to a single urban children's hospital with a diagnosis of meningitis, are there objective and readily available parameters to distinguish bacterial from aseptic meningitis and identify a very low-risk group who may be suitable for outpatient management?

DESIGN/VALIDITY: This was a retrospective cohort of patients between 29 days to 19 years of age admitted to a Children's Hospital over an 8-year period with a final diagnosis of meningitis using ICD-9 codes. In the derivation cohort 437 patients of which 82 (18.8%) had bacterial meningitis were included in the derivation cohort. Since the intention was to identify a low-risk portion of the population, those patients with clinical sepsis, immunocompromised state, who recently underwent neurosurgical procedures amongst other criteria, were excluded. Definitions of bacterial and aseptic meningitis were clear and intuitive. Candidate variables were chosen if they were objective, biologically plausible, available at patient presentation, and had been supported by prior studies.

PRIMARY RESULTS: In the combined derivation and validation cohort 696 children were identified with meningitis. 125/696 (18%) had bacterial meningitis with 63% due to Streptoccoccus pneumonia. This is a prevalence higher than population estimates, and likely reflective of the regional referral center status of the children's hospital. Candidate predictors from the univariate analysis underwent multivariate logistic regression and binary recursive partitioning analyses resulting in a weighted prediction model with 5 variables.

BACTERIAL MENINGITIS SCORE	POINTS
Positive CSF Gram Stain	2
CSF ANC ≥ 1000 cells/mm^3	1
CSF protein ≥ 80 mg/dl	1
Peripheral ANC ≥ 10,000 cells/mm^3	1
Seizure before or at the time of presentation	1
A positive outcome score is ≥1 predictor (1 point per predictor)	

A bacterial meningitis score of ≥ 1 had a sensitivity of 97.6% (91.5, 99.3%). 2 patients with bacterial meningitis were misclassified by the rule. One of these patients had received parenteral antibiotics and likely met exclusion criteria. 0.8% of patients with a bacterial meningitis score or 0 had bacterial meningitis. When applied to the validation sample, a BMS of 0 did not misclassify any patients with bacterial meningitis as having aseptic meningitis, with a negative predictive value of 100%, 95% CI 97, 100%) and specificity of 73%, 95% CI 91-100%. In the combined sample (derivation plus validation cohorts), 0.5%, 95% CI (0.06, 1.8%) of patients with a BMS of 0 had bacterial meningitis, but the confidence interval suggests this number can range slightly higher.

APPLICABILITY: Data collection for this study ended in June 2000. This is prior to the widespread use of the protein conjugate pneumococcal vaccines (Prevnar 7 (2000) and Prevnar 13 (2010)). 63% of the bacterial meningitis cases were due to Pneumococcus. With the widespread use of these vaccines the prevalence of bacterial meningitis and particular those due to gram positive organisms is expected to decrease. This is a stage IV clinical decision rule (See Appendix) which requires external validation before it can be applied clinically

AUTHOR'S CONCLUSION: "The BMS accurately identifies children at low (BMS = 0) or high (BMS >2) risk of bacterial meningitis. Outpatient management may be considered for children in the low-risk group."

POTENTIAL IMPACT: Previously, the majority of patients with meningitis were admitted to the hospital for observation and possibly empiric treatment pending cultures. Using this simple scoring system, almost 60% of the sample could have been classified as very low risk for bacterial meningitis, and a proportion of these patients may have been managed as outpatients. Given a small but potentially important misclassification rate, empiric antibiotic treatment may be considered in this subset of patients. External validation is required before this rule can be applied clinically.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

MENINGITIS:
BACTERIAL MENINGITIS SCORE VALIDATION

In pediatric patients with CSF pleocytosis who are clinically well-appearing and who could otherwise be discharged from the EmergencyDepartment does the previously derived Bacterial Meningitis Score accurately distinguish between bacterial and aseptic meningitis?

Rachel Kowalsky, M.D., MPH, Adriana Manikian, M.D.
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Nigrovic LE, Kuppermann N, Macias CG, Cannavino CR, Moro-Sutherland DM, Schremmer RD, Schwab SH, Agrawal D, Mansour KM, Bennett JE, Katsogridakis YL, Mohseni MM, Bulloch B, Steele DW, Kaplan RL, Herman MI, Bandyopadhyay S, Dayan P, Truong UT, Wang VJ, Bonsu BK, Chapman JL, Kanegaye JT, Malley R; Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics.

CLINICAL PREDICTION RULE FOR IDENTIFYING CHILDREN WITH CEREBROSPINAL FLUID PLEOCYTOSIS AT VERY LOW RISK OF BACTERIAL MENINGITIS.

JAMA. 2007 Jan 3;297(1):52-60.
PubMed ID: 17200475

STUDY DEFINITIONS	
POPULATION	Inclusion: 29 days-19 years, diagnosis of meningitis by ICD9 codes, lumbar puncture performed in ED. Exclusion: Patients with CSF pleocytosis who would require hospital admission regardless of the risk of bacterial meningitis: 1. Critical illness (defined as severely altered mental status, evidence of cerebral herniation, need for respiratory or blood pressure support), purpura 2. Presence of ventricular shunt device, recent neurosurgery, immunosuppression, 3. Bacterial infections necessitating inpatient antibiotic therapy (e.g., urinary tract infections in infants 3 months, periorbital cellulitis, deep abscess, bone or joint infections, or known bacteremia), or active Lyme disease. 4. Received oral/parenteral antibiotics within 72 hours prior to lumbar puncture. Setting: Pediatric Emergency Medicine Collaborative Research Committee of the AAP. N = 20 Emergency departments in the U.S (13 free standing pediatric centers and 3 general EDs), 1/2001-6/2004
RULE PARAMETERS	1. Positive CSF gram stain 2. CSF Absolute neutrophil count (ANC) ≥ 1000 cells/μL 3. CSF Protein ≥ 80 mg/dL 4. Peripheral Absolute neutrophil count (ANC) ≥ 10,000 cells/μL 5. History of seizure before or at the time of presentation
REFERENCE STANDARD	Meningitis: CSF pleocytosis $\nu \geq 10$ cells/μL, corrected for the presence of CSF red blood cells using a 1:500 ratio of leukocytes to erythrocytes usually found in peripheral blood) Bacterial Meningitis: 1. Positive CSF culture OR 2. CSF pleocytosis with a positive blood culture for a bacterial pathogen, OR 3. CSF pleocytosis with a positive CSF latex agglutination test for a bacterial pathogen. Contaminates: *Staphylococcus epidermidis*, *Streptococcus viridans* and *Proprionobacterium acnes* Aseptic Meningitis: CSF pleocytosis with negative bacterial cultures of blood and CSF and a negative CSF latex agglutination test (if obtained).
OUTCOME	Decision rule characteristics
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were the patients chosen in an unbiased fashion and do they represent a wide spectrum of severity of disease?	Yes. Patients were aged 29 days to 19 years who, in the ED, had received an ICD9 diagnosis of meningitis (bacterial, viral, or NOS) in 20 ED's from 1/01-6/04 AND received an LP. Complete capture was ensured by checking institutional microbiology logs. The retrospective nature of the study may lead to missed patients (especially those with aseptic meningitis).
Was there a blinded assessment of the criterion standard for all patients?	There is no blinding in this study. The authors note specifically that each investigator entered the data himself either onto a case report form or computerized database. Presumably this occurred prior to the determination of meningitis etiology. Foreknowledge of the predictors would not bias the objective CSF and culture findings that define the meningitis etiology (bacterial vs. aseptic) in the study
Was there an explicit and accurate interpretation of the predictor variables and the actual rule without knowledge of the outcome?	Yes. As this is a retrospective validation of a rule, and the investigators themselves identified the cases and entered all data in the database, it is likely that they had knowledge of the predictors and outcomes from the beginning. However, impact on the integrity of the data is probably minimal, as criteria are mainly objective and would not be subject to misclassification bias. The last variable (seizure) would be more susceptible but was rigidly defined as "any abnormal neurological activity thought to possibly be a seizure".
Was there 100% follow up of those enrolled?	This was a retrospective study that did not involve follow-up.

WHAT ARE THE RESULTS?

2,903 with CSF pleocytosis with all predictors identified
Prevalence of Bacterial Meningitis: 121/2,903 = 4.1(%)
29% S. pneumonia, 48% gram negative organisms
80% admitted (including all with bacterial meningitis)

		BACTERIAL MENINGITIS		
		YES	NO	
BACTERIAL MENINGITIS SCORE	NOT LOW RISK*	119	1,070	1,189
	LOW RISK	2	1,712	1,714
* ≥1 Predictor		121	2,782	2,903

BMS PREDICTORS (#)	BACTERIAL MENINGITIS (%)
0	0.1%
1	3%
2	27%
3	70%
≥4	95%

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)
Sensitivity: 119/121 = 98.3%, 95% CI (94.2, 99.8%) Predictive Value (+) Rule: 119/1,189 = 10%, 95% CI (8.4, 11.8%) Likelihood Ratio (+) Rule: (119/121)/(1,070/2782) 2.56, 95% CI (2.43, 2.69)
HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)
Specificity: 1.712/2.782 = 61.5%, 95% CI (59.7, 63.3%) Predictive Value (-) Rule: 1,712/1,714= 99.9%, 95% CI (99.6,100%) Likelihood Ratio (-) Rule: (2/121)/(1,712/2,782) = 0.62 = 0.03, 95% CI (0.01-0.11)
HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?
1,714/2,903 (59%) of the patients were BMS = 0 (did not have any of the rule risk parameters). If all of these patients were discharged, the admit rate would be 61%. Since the study admit rate was 80% the application of the rule could potentially reduce the admission rate by 19% (80 - 61%)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see Appendix)	☐ I ■ II ☐ III ☐ IV This is level II clinical decision rule. A level II rule has been validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. An impact analysis has not been completed. A level II rule can be used in a wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve. (See Appendix for level definitions)
Does the rule make clinical sense?	The rule may be difficult to use in the clinical setting because there are 5 components, 3 of which are numbers to memorize. However, once recalled, the rule could greatly reduce the number of aseptic meningitis cases that are needlessly admitted.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	4 of the 5 predictors are completely objective and will be easy to use in the clinical setting. Subtle seizures may not be recognized.
Is the rule applicable to the patients in my practice?	Patients were from 20 different U.S. ED's which included free standing children's hospitals as well as general hospitals. It can likely that the patient mix includes a wide range of ages, socio-economic and demographic factors, clinical settings, geographic areas and seasons.
What are the benefits of applying the rule to my patients?	1.714 of 2903 patients (59%) in this study were classified as very low risk of bacterial meningitis potentially reducing admissions.
What are the risks of applying the rule to my patients?	The rule missed two children with bacterial meningitis, both were under the age of two months. The lower limit of the 95% confidence interval for the predictive value of a negative rule was 99.6%. Therefore, 0.4% (1 in 250) of patients with no BMS risk factors could potentially have bacterial meningitis.

CLINICAL BOTTOM LINE

BACKGROUND: Patients with CSF pleocytosis are routinely admitted to the hospital because of the difficulty in distinguishing between bacterial and aseptic meningitis. Some of these patients could patients could be potentially discharged safely. The Bacterial Meningitis Score (BMS) has been previously derived and was accurate in making the distinction between bacterial and aseptic meningitis. This study attempts to validate the BMS in a retrospective cohort of patients with CSF pleocystosis.

CLINICAL QUESTION: In pediatric patients with CSF pleocytosis who are clinically well-appearing and who could otherwise be discharged from the Emergency Department does the previously derived Bacterial Meningitis Score accurately distinguish between bacterial and aseptic meningitis in a multi center, retrospective validation cohort?

DESIGN/RISK OF BIAS: This was a well-designed, multicenter retrospective cohort study that included 3,295 patients with CSF pleocytosis of which 121 (3.7%) were determined to have bacterial meningitis. There were no major validity concerns.

PRIMARY RESULTS: In this retrospective external validation of a Bacterial Meningitis Score, a BMS ≥ 1 correctly identified patients with bacterial meningitis. Sensitivity: 98.3%, 95% CI (94.2, 99.8%), Predictive Value of a Negative Rule: 99.9%, 95% CI (99.6,100%). Two infants less than 2 months of age with bacterial meningitis were misidentified by the rule. 59% of the patients did not have any BMS risk factors (BMS = 0). If all of these patients were discharged the admit rate would be 61%. Since the study admit rate was 80% the application of the rule could reduce the admission rate by 19% (80 - 61%)

BACTERIAL MENINGITIS SCORE	ADJUSTED OR (95% CI)
Positive CSF gram stain	653.7 (216.6, 1,972.8)
CSF Absolute neutrophil count (ANC) ≥ 1000 cells/μL	8.0 (3.8, 17.0)
CSF Protein ≥ 80 mg/dL	12.2 (5.7, 26)
Peripheral Absolute neutrophil count (ANC) ≥ 10,000 cells/μL	4.1 (2.2, 8.0)
History of seizure before or at the time of presentation	3.7 (1.0, 13.4)
A POSITIVE score is the PRESENCE of ANY (≥ 1) of the above PREDICTORS A NEGATIVE score is the ABSENCE of ALL (0) of the above PREDICTORS	

APPLICABILITY: The BMS shouldn't be used in infants ≤ 2 months as their risk for SBI including bacterial meningitis is higher than the rest of this population even if they meet low risk criteria

Although prospective external validation is preferable, given the extremely low incidence of bacterial meningitis in the universal HIB and Prevnar immunization era, it would be extremely difficult and time-consuming to collect enough patients for a meaningful analysis.

This is level II clinical decision rule. A level II rule has been validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. An impact analysis has not been completed. A level II rule can be used in a wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve.

AUTHOR'S CONCLUSION: "This large, multicenter study validates the Bacterial Meningitis Score prediction rule in the era of conjugate pneumococcal vaccine as an accurate decision support tool. The risk of bacterial meningitis is very low (0.1%) in patients with none of the criteria. The Bacterial Meningitis Score may be helpful to guide clinical decision making for the management of children presenting to emergency departments with CSF pleocytosis."

POTENTIAL IMPACT: It appears reasonable to use the BMS to identify select patients greater than 2 months of age with CSF pleocytosis who are at very low risk for bacterial meningitis and who could potentially be safely managed as outpatients. The authors emphasize that the rule is an assistive rule and should not supplant careful clinical assessment.

The role of parenteral antibiotics pending negative cultures was not assessed in this study. The authors make the following recommendations based on the patient not meeting any of the studies exclusion criteria, are well appearing and with follow-up assured the next day.

Given the declining prevalence of bacterial meningitis it may be difficult to complete an impact analysis of the bacterial meningitis score. The epidemiology of bacterial meningitis is also changing. Approximately 30% of bacterial meningitis in this study was due to S. pneumoniae. If the prevalence of S pneumoniae meningitis continues to decrease with the use of the 13 valent pneumococcal conjugate vaccine the accuracy of the rule may need to be re-evaluated. As the proportion of bacterial meningitis due to gram negative organisms increases the performance of some of the rules biomarkers may suffer as gram negative organisms tend to suppress biomarkers.

AGE	BMS RISK FACTORS (#)	DISPOSITION	ANTIBIOTICS
< 2 months	0	Admission	YES
	≥ 1	Admission	YES
≥ 2 months	0	Option A: Admission Option B: Discharge	YES or NO YES or NO (Strongly Consider YES)
	≥ 1	Admission	YES

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

MENINGITIS:
BACTERIAL MENINGITIS SCORE META-ANALYSIS

In children with suspected meningitis and CSF pleocytosis what are the rule characteristics and potential impact on resource utilization of the bacterial meningitis score?

Alvira Shah, M.D., Inna Elikashvili, D.O.
February 4, 2014

Nigrovic LE, Malley R, Kuppermann N.

META-ANALYSIS OF
BACTERIAL MENINGITIS SCORE VALIDATION STUDIES

Arch Dis Child. 2012 Sep;97(9):799-805.
PubMed ID: 22764093

STUDY DEFINITIONS	
POPULATION	Inclusion: Eligible studies included children younger than 18 years of age, sufficient information to calculate the Bacterial Meningitis Score. Exclusion: Patients used for the decision rule derivation study, patients pre-treated with antibiotics before lumbar puncture. Exclusion criteria for individual studies were variable (Table 4) Setting: Patients from the U.S., Western Europe and Argentina
INTERVENTION	Bacterial meningitis score
CONTROL	CSF culture positive for a bacterial pathogen, Inclusion varied by study whether positive CSF Gram stain, latex agglutination test, CSF bacterial PCR test or CSF pleocytosis with a positive blood culture but negative CSF culture was considered bacterial meningitis (Table 4)
OUTCOME	Rule characteristics Potential impact on resource utilization Sensitivity calculated for all study types (8), Specificity for case-control and cohort (7), Predictive values calculated only for cohort studies (6)
DESIGN	Meta-analysis of clinical decision rule validation studies Case series (1), case-control (1), retrospective cohort (5) prospective cohort (1)

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review include explicitly and appropriate eligibility criteria?	Yes. In the methods section, they describe the search of published bacterial meningitis score (BMS) validation studies between Oct 2002-March 2012, using Medline and EMBase. They excluded studies where they could not verify the study procedures. They included patients < 18 years with sufficient information to calculate the BMS. The excluded patients from the rule derivation study and those who received antibiotics prior to lumbar puncture.
Was biased selection and reporting of studies unlikely?	Yes. In retrospective studies (7 out of 8 in this meta-analysis) there is more risk for bias compared to prospective studies. There was no assessment for publication bias.
Were the primary studies of high methodologic quality?	Yes. They assessed the quality of included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) instrument. (Table 3). The included studies were of high quality. Only the Dubos study from 2006 had risk of bias and applicability concerns secondary to patient selection and questionable reference standard.
Were assessment of studies reproducible?	No. No measure of interrater reliability is provided for study inclusion or study quality.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

For sensitivity, all studies have a similar point estimate (Figure 1: Forest Plot). The Cochrane Q p value is 0.88 indicating no heterogeneity (qualitative assessment of heterogeneity: null hypothesis = no heterogeneity) The I^2 = 0 indicating no heterogeneity (quantitative assessment of heterogeneity < 0.25 = small, 0.25-0.5 = moderate and > 0.5 = large heterogeneity)

This meta-analysis includes 8 studies. (Table 5)
Initial n = 5,312. Final n = 4,896 (416 excluded)

	BACTERIAL MENINGITIS	ASEPTIC MENINGITIS	
Not Low Risk (BMS ≥ 1)	1,224	1,389	2,613
Very Low Risk (BMS = 0)	9	2,274	2,283
	1,233	3,663	4,896

Prevalence of Bacterial Meningitis = 1233/4896 = 25.2%

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

Sensitivity: 1,224/1,23 = 99.3%, 95% CI (98.7, 99.7%)
Predictive Value (-) Rule: 2,274/2,283 = 99.6%, 95% CI (99.3, 99.8%)
Likelihood Ratio (+) Rule: 2.6, 95% CI (2.5, 2.7)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

Specificity: 2,274/3,663 = 62.1%, 95% CI (60.5, 63.7%)
Predictive Value (+) Rule: 28.1%, 95% CI (22.6, 33.9%).
Likelihood ratio (-) Rule: 0.01, 95% CI (0.01, 0.02)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

2,283 patients of 4,896 (47%) would be considered at very low risk of bacterial meningitis (BMS = 0). These patients could potentially be discharged.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see appendix)	☐ I: Impact Analysis ☐ III: Validated Narrowly ☑ II: Validated Broadly ☐ IV: Derived Only This is a meta-analysis of validated clinical decision rule studies. Combining these studies broadly validates the rule (Level II). A level II rule can be used in a wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve. An impact analysis would be required to make this a Level I rule.
Does the rule make clinical sense?	Yes. The rule makes clinical sense. It includes 4 objective laboratory values and one clinical variable: seizures. Other clinical variables such as season of illness and duration of fever were not found to be significant predictors in the derivation of the rule.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	This study included a broad range of patients from the US, Argentina and Europe. The bacteriology of meningitis may vary in different settings as vaccination strategies differ. The 2007 Nigrovic Study included approximately ¾ of the patients in this meta-analysis and is the only study setting that had implemented the pneumococcal vaccine (Prevnar 7). The implementation of Prevnar 13 and the meningococcal vaccine may further reduce the prevalence of bacterial meningitis
Is the rule applicable to the patients in my practice?	The potential benefit of applying the rule would be a reduction in those admitted for bacterial meningitis that have aseptic meningitis. The authors recommend treatment with a long acting antibiotic and close clinical follow-up of those discharged.
What are the benefits of applying the rule to my patients?	9 patients with bacterial meningitis were misidentified as being of very low risk (Table 6). 3 of these patients were less than 2 months of age and would have been excluded as per author recommendations. 3 additional patients with Neisseria had petechiae or purpura on examination. The remaining 3 patients with meningococcal meningitis would have been missed by using the rule (3/2,283 = 0.18%).
What are the risks of applying the rule to my patients?	This study included a broad range of patients from the US, Argentina and Europe. The bacteriology of meningitis may vary in different settings as vaccination strategies differ. The 2007 Nigrovic Study included approximately ¾ of the patients in this meta-analysis and is the only study setting that had implement the pneumococcal vaccine (Prevnar 7). The implementation of Prevnar 13 and the meningococcal vaccine may further reduce the prevalence of specific organisms.

CLINICAL BOTTOM LINE

BACKGROUND: The bacterial meningitis score is a previously derived and validated clinical prediction rule that identifies children with CSF pleocytosis who are at very low risk for bacterial meningitis.

CLINICAL QUESTION: In children with suspected meningitis and CSF pleocytosis what are the rule characteristics and potential to impact resource utilization of the bacterial meningitis score?

DESIGN/RISK OF BIAS: The studies included in the meta-analyses were of high quality, and there are no major validity concerns in the methodology of the meta-analysis. Measurement of interrater reliability for study inclusion or study quality would have been helpful.

PRIMARY RESULTS: From 8 studies, 5312 patients were identified, of whom 4896 (92%) had sufficient clinical data to calculate the Bacterial Meningitis Score. Bacterial meningitis was diagnosed in 1242 children (23%). The combined rule characteristics of the Bacterial Meningitis Score are: Sensitivity 99.3%, 95% CI (98.7, 99.7%), Specificity 62.1%, 95% CI (60.5, 63.7%), Negative predictive value 99.7%, 95% CI (99.3, 99.9%), Positive Likelihood ratio 2.6, 95% CI (2.5, 2.7), Negative Likelihood ratio 0.01, 95% CI (0.01, 0.02).

The potential benefit of the rule is to discharge those identified as at very low risk for bacterial meningitis. The rule was negative in 47% of the patients. Use of the bacterial meningitis score could potentially reduce admission by 47%.

BACTERIAL MENINGITIS SCORE	EXCLUSION CRITERIA
1. Positive CSF Gram Stain	< 2 months of age
2. CSF ANC ≥ 1000 cells/mm^3	Purpura
3. CSF protein ≥ 80 mg/dL	Immunodeficiency
4. Peripheral ANC ≥10,000 cells/mm^3	Prior antibiotics
5. H/O seizure before or at the time of presentation	Critical Illness
A positive BMS is ≥1 predictor	Neurosurgery or shunt

APPLICABILITY: This rule makes clinical sense and is applicable to patients we see in the emergency department. It can be applied to children > 2 months of age, that are clinically well-appearing and not immunocompromised. (see rule summary below). The rule can be applied easily since we routinely obtain blood and CSF on patients with suspected meningitis, and 4 out the 5 rule components are lab values The single clinical parameter, associated seizures, can also be easily obtained.

The rule is at Level II of development (see appendix below) with broad validation of primarily retrospective data. Level II rules can be used in a wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve. In order to become a Level I, the rule's impact needs to be studied by using it prospectively and determining if the rule characteristics and reduction in resource utilization stay the same.

AUTHOR'S CONCLUSION: "In summary, the Bacterial Meningitis Score performed with a high degree of diagnostic accuracy in eight validation studies. This score, in conjunction with clinical judgment can identify children with CSF pleocytosis who are at very low risk for bacterial meningitis. To minimize misclassification of children with bacterial meningitis, we recommend that the Bacterial Meningitis Score only be applied to non-ill-appearing children older than 2 months, who do not have either petechiae or purpura on examination and have not been pretreated with antibiotics. For those children at very low risk, who have adequate clinical follow-up, clinicians could consider outpatient treatment after administration of a long-acting parenteral antibiotic. Future studies should focus on the implementation of the Bacterial Meningitis Score to prospectively identify children who are at very low risk of bacterial meningitis".

POTENTIAL IMPACT: The material meningitis score when used with the exclusion criteria correctly identifies a group with CSF pleocystosis at low risk of bacterial meningitis. Approximately half of the patients could potentially be discharged. 9 out of 4896 patients with CSF pleocytosis who had bacterial meningitis were missed by the rule (0.18%). Of the 9 missed, 5 would have been identified by the exclusion criteria. Administering a long acting antibiotic and following those at very low risk clinically the next day can potentially lessen the consequence of discharging the rare very low risk patient with bacterial meningitis. It is important to remember that the rule does not exclude the possibility of herpes simple virus encephalitis, Lyme meningitis or Mycobacterium tuberculosis meningitis and these would require treatment.

SEE ALSO:

Nigrovic LE, Kuppermann N, Malley R.
Development and Validation of a Multivariable Predictive Model to Distinguish Bacterial From Aseptic Meningitis in Children in the Post-Haemophilus Influenzae Era.
Pediatrics. 2002 Oct;110(4):712-9. PubMed ID: 12359784

Nigrovic LE, Kuppermann N, Macias CG, Cannavino CR, Moro-Sutherland DM, Schremmer RD, Schwab SH, Agrawal D, Mansour KM, Bennett JE, Katsogridakis YL, Mohseni MM, Bulloch B, Steele DW, Kaplan RL, Herman MI, Bandyopadhyay S, Dayan P, Truong UT, Wang VJ, Bonsu BK, Chapman JL, Kanegaye JT, Malley R; Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics.
Clinical Rediction Rule for Identifying Children with Cerebrospinal Fluid Pleocytosis at Very Low Risk of Bacterial Meningitis.
JAMA. 2007 Jan 3;297(1):52-60. PubMed ID: 17200475

APPENDIX: CLINICAL DECISION RULES STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

MIGRAINE HEADACHE:
ED THERAPY

In pediatric patients 7 to 18 years old with a migraine headache in the emergency department (ED) what is the most effective treatment regimen to prevents revisits to the ED?

Sheri-Ann Wynter, M.D., Karen Goodman, M.D.
March 2015

Bachur RG, Monuteaux MC, Neuman MI.

A COMPARISON OF ACUTE TREATMENT REGIMENS FOR MIGRAINE IN THE EMERGENCY DEPARTMENT.

Pediatrics. 2015 Feb;135(2):232-8.
PubMed ID: 25624377

STUDY DEFINITIONS	
POPULATION	Inclusion: Children aged 7-18 years old, evaluated and discharged with a principle diagnosis of migraine Exclusion: Complex comorbid condition (congenital heart disease, myopathies, cystic fibrosis, sickle cell) Patients who were transfers from other institutions Setting: 35 Pediatric EDs (Pediatric Health Information System database). 2009-2012
INTERVENTION	Dopamine receptor antagonists Diphenhydramine Ondansetron Antiepileptics Corticosteroids Opioids Triptans Dihydroergotamine mesylate Regimens with various combinations of the above Medications taken prior to arrival could not be assessed form the database used.
CONTROL	Non-opioid analgesics
OUTCOME	Primary Outcome: Revisits to the ED within 3 days for patients discharged from index encounter Secondary Outcomes: Discharge rate from ED Adverse events
DESIGN	Retrospective cohort

ARE THE RESULTS VALID? (COHORT STUDY)

DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	Yes. The logistic regression equation used covariates that were later adjusted in the determination of the primary outcome. These covariates include age, gender, race, insurance status, IVF, LP, CT, MRI and severity classification system. However, medications taken prior to arrival, pain score, ED length of stay and prior history of migraine were not evaluated.
Were the circumstances and methods for detecting the outcome similar?	Yes. All revisits within the 3-day window were included, regardless of the principal diagnosis or disposition associated with the revisit. Only the first revisit was included in the analysis in cases where there were more than one revisits.
Was follow-up sufficiently complete?	No. Follow-up was only done for those who returned to the ED (not for those who did not have a revisit), and revisits were limited to returns to the same institution. Visits to other hospitals or primary care providers could not be determined.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

N = 27,317 discharged patients (90% of total patients)
5.5% with a revisit.

See Table 3
The association between exposure (treatment regimen) and outcome (3-day revisit rate) is presented as an odds ratio.

It is strongest for treatment regimens that included diphenhydramine (clinically significant for non-opioid analgesics, dopamine antagonists, and diphenhydramine compared with non-opioid analgesics and dopamine antagonists alone), atypical medications such as AEDs, and for “other permutations.”

HOW PRECISE IS THE ESTIMATE OF THE RISK?

The estimate of the risk of ED revisit is most precise for two compared regimens. The confidence intervals are statically significant for two of the medication regimens:
1. Dopamine antagonists with diphenhydramine when compared to without diphenhydramine
2. Metoclopramide when compared to Prochlorperazine.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	See Table 1 for demographic data. Similar age groups, predominantly female (67%), and most were treated with intravenous fluids (55%). However, 17% had neuro- imaging and 20% received no medications
Was follow-up sufficiently long?	Follow-up was not done for patients who did not have a revisit to the ED within three days.
Is the exposure similar to what might occur in my patient?	Yes. Non-opioid analgesics and Ondansetron are commonly used. However, imaging is not as common.
What is the magnitude of the risk?	Adverse events of treatment were not in this study.
Are there any benefits that are known to be associated with exposure?	Decreased revisit to the ED within three days is known to be associated with a variety of treatment regimens.

CLINICAL BOTTOM LINE

BACKGROUND: There is no standard of care or existing guidelines for treating migraines in children. As a result, there is large variation in care. This article compares various therapeutic regimens for migraines in children presenting to the emergency department using a retrospective design. The authors seek to determine which regimen is most effective, as determined by which is associated with the least ED revisits within three days from the initial visit.

CLINICAL QUESTIONS: In pediatric patients 7 to 18 years old with a migraine headache in the emergency department what is the most effective treatment regimen that prevents revisits to the ED?

DESIGN/VALIDITY: This was a retrospective cohort study from an existing children's hospital database including 32,124 patients with a diagnosis of migraine. There are some validity concerns, however, as the study is only able to follow-up those patients who returned to the ED at the same institution where they were initially seen. In addition, ED revisits were defined as within 3 days of the initial visit, regardless of the reason for revisit, and regardless of the number of times revisits occurred. The use of administrative data limited determination of more specific details particularly with relevant patient characteristics and important clinical outcomes such discharge rate from the initial ED visit and adverse events.

PRIMARY RESULTS: ED revisits were associated with use of diphenhydramine in a migraine therapy regimen, use of atypical medications such as AEDs, and use of metoclopramide in comparison to Prochlorperazine. However, it is unclear whether diphenhydramine was used prophylactically for patients to prevent extrapyramidal symptoms (EPS), or after demonstration of symptoms.

APPLICABILITY: The use of a large multicenter database likely makes the study's results applicable to those meeting the studies inclusion and exclusion criteria. This study may not be generalizable to all populations as determined by the limited demographic data reported.

AUTHORS CONCLUSIONS: "The majority of children with migraines are successfully discharged from the ED and only 1 in 18 required a revisit within 3 days. Prochlorperazine appears to be superior to Metoclopramide in preventing a revisit, and diphenhydramine use is associated with increased rates of return."

POTENTIAL IMPACT: Although there did appear to be a demonstrated association between certain treatment regimens and ED revisit rate, there are some limitations to the translation of this data to clinical care as described above. Providers may consider using Prochlorperazine instead of Metoclopramide based on these results, but there is not sufficient data to recommend limiting the use of diphenhydramine.

MIGRAINE HEADACHE: LOW DOSE PROPOFOL

In pediatric patients, 7 to 19 years of age with an acute migraine presenting to the emergency department, does low dose Propofol titrated to effect when compared to a standard therapy regimen of nonsteroidal anti-inflammatory, antihistaminic and antidopaminergic medications, have more effective pain reduction after initial treatment?

Guillermo De Angulo, M.D., Inna Elikashvili, M.D.

April 2018

Sheridan DC, Hansen ML, Lin AL, Fu R, Meckler GD

LOW-DOSE PROPOFOL FOR PEDIATRIC MIGRAINE: A PROSPECTIVE, RANDOMIZED CONTROLLED TRIAL.

J Emerg Med. 2018 Feb 15, (18) 30015-5.
PubMed ID: 29456086

STUDY DEFINITIONS	
POPULATION	Inclusion: Ages 7-19 years Presenting to the ED with an acute headache considered to be a migraine by the treating physician (patient with or without a prior history of migraines) Visual Analog Score (VAS) pain score ≥ 6 (out of 10) Exclusion: Known allergy to any study medication Signs of a secondary headache Acute head injury History of tumor, malignancy Major surgery within previous 7 days Intracranial shunt Chronic lung disease Congenital/Acquired heart disease with poor cardiac function or single ventricle Known renal failure. Setting: Two tertiary care Pediatric EDs in close proximity to each other.
INTERVENTION	0.25 mg/kg (maximum 30 mg) Propofol IV every 5 minutes until resolution of pain (VAS ≤ 4) with a maximum of 5 doses Propofol required deep sedation monitoring
CONTROL	Ketorolac: 0.5 mg/kg IV (maximum dose 30 mg IV) Diphenhydramine: 1 mg/kg IV (maximum dose 50 mg IV) Metoclopramide: 0.1 mg/kg IV (maximum dose 10 mg IV)
CO-INTERVENTION	Normal Saline Bolus 20 ml/kg IV (maximum of 1 liter) prior to medications Rescue therapy at MD discretion
OUTCOME	Primary Outcome: Pain reduction after initial treatment (↓ VAS and % ↓) Secondary Outcomes: Treatment Failure: Propofol Group: VAS pain score > 4 after 5 boluses (25 minutes) Standard Group: VAS score > 4 at 1 hour or after awakening if > 1 hour Total Length of Stay: ED arrival to ED discharge Treatment Length of Stay: Time from 1st study medication to ED discharge Return ED visits Rebound headache at 24 hours follow up (VAS > ED Discharge VAS) Adverse Reactions: Extrapyramidal reactions, significant changes in vital signs: hypotension, hypoxemia or respiratory depression.
DESIGN	Pragmatic, Randomized Control Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were pre-randomized and split between the two hospitals prior to the start date.
Was randomization concealed?	Yes. It appears that the provider did not have the ability to change the group allocation. The study sequentially utilized opaque folders.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. (Table 1). However, the two prognostic factors differed between the groups were personal history of migraines and daily prophylaxis for migraines. A higher percentage of the patients in the Propofol group (86.7% vs 66.7%) had a prior history of migraines and the standard group had a higher percentage of patient's that took daily migraine prophylaxis (25% vs 13.3). The author's do not perform a subgroup or regression analysis to account for these differences.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study was not blinded. After allocation, it was not feasible to blind the treating physician to the medication group due to the difference in medication dosing frequency (repeated dosing every 5 minutes for Propofol and a single dose of 3 different medications in the standard therapy group). Because physician blinding was not feasible the trial is defined as pragmatic. Patients were not blinded to the medications though they were not overtly told what medications they were receiving.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Discharge patients were contacted by telephone at 18-24 hours. 60 of 66 patients were discharged. The proportion of discharged patients who were contacted was not presented though Figure 1 indicates that all 66 patients were included in the analysis.
Were patients analyzed in the groups to which they were randomized?	Yes. Though not explicitly stated it appears that the patients were analyzed based on the intention to treat principle. 74 patients were randomized though 6 patients were excluded for repeat visits. The remaining 66 patients were included in the analysis. It was not explicitly stated if the patients received the study medications as intended.
Was the trial stopped early?	Yes. The sample size indicated a need for 74 patients while only 66 were included in the analysis. This could potentially underpower the study thought the difference in the primary outcome (8%) was less than the 20% proposed by the authors as clinically significant and a much larger sample size would have been required for an 8% difference to be statistically significant.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

There was no statistically significant difference in any of the outcomes with the exception of a 41% more patients in the standard care group experienced rebound headaches. However, the small sample size may allow for clinically significant differences that are not statistically significant.

	STANDARD CARE[1] (n=36)	**LOW DOSE PROPOFOL[2]** (n=30)
Presentation VAS (Mean±SD)	8.3 ± 1.4	7.9 ± 1.1
Pain Reduction (↓ VAS)	4.83	4.03
Proportion Pain Reduction[3]	59%	51%
Treatment Success	72.2%	73.3%
Required Rescue Medication	22.2%	36.7%
Rebound Headache[4]	66.7%	25.0%
Adverse Events	Extrapyramidal (n=3)	Desaturation (n=1)
Return to ED	6.5%	3.7%
LOS (Medication → D/C)	111 minutes	79 minutes
LOS (ED Arrival → D/C)	219 minutes	229.5 minutes

1. Ketorolac + Diphenhydramine + Metoclopramide
2. Mean Propofol dose: 3.3 ± 1.3 boluses (0.825 ± 0.325 mg/kg)
3. The authors considered a 20% difference in pain reduction to be clinically significant
4. Only statistically significant difference. No risk difference with 95% CI presented

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence intervals for the mean difference and risk difference were not provided.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. The study's population is similar to ours. In our patient population, we treat many patients with and without a prior history of migraines.
Were all patient important outcomes considered?	Yes. The authors included a number of patient and disease oriented outcomes. However, the majority of the migraine literature uses pain relief at two hours as a primary outcome limiting the ability to compare this study's results. In addition, a 15 mm difference is VAS score is typically considered statistically significant and the proportion of patients meeting this criteria was not presented.
Are the likely treatment benefits worth the potential harm and costs?	Propofol did not demonstrate a benefit over standard therapy other than to decrease the rate of rebound headaches. There was a non-statistically significant 30 minute decrease in time from medication administration to discharge in the Propofol group but no difference in the total ED length of stay. Propofol requires more physician time at the bedside to administer Propofol every 5 minutes as needed and required deep sedation monitoring. 1 patient in the Propofol group desaturated but did not require intervention while 3 patients in the standard therapy group had extrapyramidal symptoms.

CLINICAL BOTTOM LINE

BACKGROUND: Migraines are a common occurrence within the pediatric population that leads to emergency department visits. There are several therapeutic options for acute treatment including oral, intranasal to intravenous medications. Standard initial therapy often consists of non-steroidal anti-inflammatory, anticholinergics, and dopamine antagonists. This regimen has the potential for extrapyramidal reactions. There is some data supporting the efficacy of sub-anesthetic doses of Propofol for refractory headaches. Though the mechanism of action of Propofol is not clear, Propofol has a more rapid onset than traditional medications and the potential to decrease the ED length of stay. In addition, Propofol can avoid the risk of extrapyramidal symptoms associated with traditional antidopaminergic medications.

CLINICAL QUESTION: In pediatric patients, 7 to 19 years of age with an acute migraine presenting to the emergency department, does low dose Propofol titrated to effect when compared to a standard therapy regimen of nonsteroidal anti-inflammatory, antihistaminic and antidopaminergic medications, have more effective pain reduction after initial treatment?

DESIGN/VALIDITY: This was a prospective randomized controlled trial that included 66 patients in the primary analysis. Patients were randomized to receive low dose propofol titrated to effect or standard therapy consisting of a regimen of Ketorolac, Diphenhydramine and Metoclopramide. The study was considered pragmatic in that the difference in delivery of medications could not be blinded and that patients with and without an established migraine diagnosis were included. This could potential underestimate the effect of therapy in both groups

There are a number of potential biases in the study's design. Treatment failure was assessed at a different time interval in the two study groups. Treatment failure in the Propofol group was defined as a VAS pain score > 4 after 5 boluses (25 minutes). Treatment failure in the Standard group was defined as a VAS score > 4 at 1 hour or after awakening if the patient was sleeping at 1 hour. Two prognostic factors differed between the groups; personal history of migraines and daily prophylaxis for migraines. A higher percentage of the patients in the Propofol group had a prior history of migraines (86.7% vs 66.7%) and the Standard treatment group had a higher percentage of patient's that took daily migraine prophylaxis (25% vs 13.3%). The authors state that "there was no association between either of these characteristics and the primary outcome. Therefore, we did not control for any patient characteristics in the final analysis, and all final analyses were bivariate comparisons of each outcome by treatment group". The study may have benefited from a subgroup or regression analysis to account for these differences.

The authors considered a number of patient and disease oriented outcomes. However, the majority of the migraine literature uses pain relief at two hours as a primary outcome limiting the ability to compare this study's results to the existing literature. In addition, a 15 mm reduction is VAS score is typically considered statistically significant in the pain literature and the proportion of patients meeting this criteria was not presented.

PRIMARY RESULTS: There was no statistically significant difference in the outcomes with the exception of 41% more patients in the standard care group experienced rebound headaches.The 72.2% treatment success rate in the standard care group seems somewhat low. The small sample size may allow for clinically significant differences that are not statistically significant. In the discussion, the authors state that “based on these results, larger studies are required to confirm noninferiority of LDP to current ST.” This statement is somewhat misleading as the author’s sample size determination was based on a superiority hypothesis and neither a proposed non-inferiority margin or confidence intervals around the risk or mean differences were presented.

	STANDARD CARE[1] (n=36)	**LOW DOSE PROPOFOL[2]** (n=30)
Presentation VAS (Mean±SD)	8.3 ± 1.4	7.9 ± 1.1
Pain Reduction (↓ VAS)	4.83	4.03
Proportion Pain Reduction[3]	59%	51%
Treatment Success	72.2%	73.3%
Required Rescue Medications	22.2%	36.7%
Rebound Headache[4]	66.7%	25.0%
Adverse Events	Extrapyramidal (n=3)	Desaturation (n=1)
Return to ED	6.5%	3.7%
LOS (Medication→D/C)	111 minutes	79 minutes
LOS (ED arrival→D/C)	219 minutes	229.5%

1. Ketorolac + Diphenhydramine + Metoclopramide
2. Mean Propofol dose 3.3 ± 1.3 boluses (0.825 ± 0.325 mg/kg)
3. The authors considered a 20% difference in pain reduction to be clinically significant
4. Only statistically significant difference. No Risk difference with 95% CI presented

APPLICABILITY: This study was conducted at two tertiary care pediatric emergency departments likely making the study’s results generalizable to patients in that setting. Other setting would not generally be able to administer Propofol unless providers were credentialed in deep sedation. I addition, the requirement for deep sedation monitoring may not allow for Propofol use in many EDs.
The inclusion criteria allowed for patients with and without a prior history of migraines to be enrolled. A larger sample size may have allowed for a subgroup analysis.

AUTHOR’S CONCLUSION: “In this study, LDP was not significantly better than ST for pain reduction in pediatric migraine, but did result in fewer rebound headaches at 24 h and showed a trend to- ward shorter median LOS from drug administration to disposition. Larger studies are needed to confirm the non-inferiority of LDP to ST, to determine the safety of LDP, and to determine optimal dosing and necessary levels of monitoring at these doses”.

POTENTIAL IMPACT: The use of low dose Propofol did not result in pain reduction compared to standard therapy. The only statistically significant finding was fewer rebound headaches in low the low dose propofol group. The small sample size (n=66), the many potential validity concerns and need for deep sedation monitoring limits the application of Propofol at this time. Further studies are needed to explore the potential benefits of Propofol for migraines.

MIGRAINE HEADACHE: THERAPY META-ANALYSIS

In adult patients with criteria defined migraine headache is Metoclopramide (Reglan) effective when compared to Placebo in relieving headache pain?

Ramona Warren M.D., Adriana Manikian, M.D.
September 2005

Colman I, Brown MD, Innes GD, Grafstein E, Roberts TE, Rowe BH.

PARENTERAL METOCLOPRAMIDE FOR ACUTE MIGRAINE: META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

BMJ. 2004 Dec 11;329(7479):1369-73.
PubMed ID: 15550401

STUDY DEFINITIONS	
POPULATION	Inclusion: Studies: Randomized controlled trials, parenteral metoclopramide for acute migraine (criteria to distinguish migraine from other types of headache), adults, acute care setting (emergency department, headache clinic). Exclusion: None specified Setting: 13 studies, 17 comparisons due to multiple study arms, 1980-2001
INTERVENTION	Metoclopramide (vs 1,2, 3 below) or Metoclopramide combinations (vs 4 below)
CONTROL	1. Placebo 2. Anti-emetics 3. Non-anti-emetics 4. Other agents
OUTCOME	Primary Outcome: Headache relief at the time closest to two hours 1. Self-reported complete relief of headache 2. Significant reduction in headache pain (moderate or severe to mild or none) 3. Reduction in headache pain based on a 100 mm visual analogue scale. Secondary Outcomes: 1. Improvement in functional status or ability 2. Relapse of migraine within 48 hours 3. Reduction in nausea 4. Number of co-intervention (“rescue”) drugs required 5. Adverse events associated with treatment.
DESIGN	Systematic review and meta-analysis of randomized clinical trials

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review explicitly address a sensible clinical question?	Yes. The questions seemed appropriately focused. Included studies comparing Metoclopramide alone compared to Placebo, anti-emetics and non-anti-emetics or Metoclopramide in combination compared to other agents.
Was the search for relevant studies detailed and exhaustive?	Yes. The search included Cochrane, Mediine, EMBase, LILACS, CINAHL, proceedings of meetings, websites, expert counsel. Search terms were headache, migraine, metoclopramide, Maxeran, Reglan, Maxolon. It is unclear if non-English language studies were assessed for inclusion. There was no assessment for publication bias.
Was the risk of bias of the primary studies assessed?	No. 13 eligible studies were included 7/13 (54%) with an Jadad 3 or better (54%) with 3 being the lower limit for a high-quality study.
Were the selection and assessment of studies reproducible?	Yes. Two independent reviewers reviewed the articles for inclusion. Differences were resolved by consensus. It is unclear if more than 1 reviewer was involved in determining the Jadad quality score. No measure of the reproducibility of study inclusion or quality was presented.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

Studies were very heterogeneous. A meta-analysis was only possible on three studies comparing Metoclopramide to Placebo.

WHAT ARE THE OVERALL RESULTS OF THE REVIEW?

Odds Ratio (Metoclopramide/Placebo)
N = 5 studies, 3 studies in meta-analysis (185 patients)
Reduction in headache pain: OR 2.84,95% CI(1.05, 7.68) Require rescue drugs: OR 0.21, 95% CI (0.05, 0.85)
2/5 studies reported relapse
2/5 studies reported adverse events

DID THE REVIEW ADDRESS CONFIDENCE IN EFFECT ESTIMATES

The confidence intervals for the odds ratios presented are very wide as a result of the small sample size.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were all patient-important outcomes considered?	No. Duration of symptoms and rebound headache were not addressed. Adverse events were not consistently reported.
Are any postulated subgroup effects credible?	A planned sensitivity analysis based on study quality was not conducted due to the small number of studies included in the meta-analysis.
What is the overall quality of the evidence?	This is low quality evidence. Only 3 studies with 185 patients comparing Metoclopramide to Placebo were included in a meta-analysis. There studies had Jadad quality scores of 3, 3 and 4.
Are the benefits worth the costs and potential risks?	Metoclopramide is desirable since it is both non-narcotic and antiemetic. Is less expensive compared to some alternative treatments. Without an adequate assessment of risks it is difficult to put potential benefits in context.

CLINICAL BOTTOM LINE

BACKGROUND: The optimal medication regimen for safe and efficient control of migraine headache pain is unknown. Metoclopramide for the treatment of migraine headache has the benefit of being a non-narcotic agent with antiemetic properties. Metoclopramide may, however, have less beneficial effects on nausea than other antiemetics and can be associated with dystonic reactions.

CLINICAL QUESTION: In adult patients with criteria defined migraine headache is Metoclopramide (Reglan) effective when compared to placebo in relieving headache pain?

DESIGN/RISK OF BIAS: Overall study quality was poor. 7/13 (54%) of studies had a Jadad quality score of 3 or higher with 3 considered the lower limit of a high-quality study design. Due to the heterogeneity of the included studies, pooled analysis of the data was only possible for studies comparing metoclopramide to placebo. In addition to the heterogeneity of study results there was significant differences in study methodology including different study outcomes and limited reporting of adverse events.

PRIMARY RESULTS: In the 3 studies comparing Metoclopramide to Placebo there was a statistic significant reduction in headache pain with Metoclopramide (OR 2.84, 95% CI (1.05, 7.68)) and patients receiving Metoclopramide less frequently required additional rescue drugs: OR 0.21,95% CI (0.05, 0.85). It is important to note that “significant reduction in headache pain” does not necessarily imply the resolution of headache pain. There was insufficient data to compare adverse events.

APPLICABILITY: These studies included only adult patients. The effects of metoclopramide may be different in children. Many patient oriented outcomes were not address by the meta-analysis.

AUTHOR’S CONCLUSION: “Metoclopramide is an effective treatment for migraine headache and may be effective when combined with other treatments. Given its non-narcotic and antiemetic properties, metoclopramide should be considered a primary agent in the treatment of acute migraines in emergency departments.”

POTENTIAL IMPACT: This study should have little impact on current practice. The one question that they could answer in both a systematic review and meta-analysis compared the efficacy of Metoclopramide to Placebo. This is not a clinically question. Placebo is not an ethical option in treating pain. A direct comparison of Metoclopramide to a specific medication could assist in clinical decision making.

STATUS EPILEPTICUS:
MIDAZOLAM VS DIAZEPAM META-ANALYSIS

In children and young adults in status epilepticus
is non-intravenous Midazolam superior
to intravenous or rectal Diazepam
as first line therapy for seizure cessation?

Carrie Danziger, M.D.
April 2012

McMullan J, Sasson C, Pancioli A, Silbergleit R.

MIDAZOLAM VERSUS DIAZEPAM FOR THE TREATMENT OF STATUS EPILEPTICUS IN CHILDREN AND YOUNG ADULTS: A META-ANALYSIS.

Acad Emerg Med. 2010 Jun;17(6):575-82.
PubMed ID: 20624136

STUDY DEFINITIONS	
POPULATION	Inclusion: Studies comparing non-intravenous Midazolam to intravenous or non-intravenous Diazepam for status epilepticus in pediatric and adult patients. CONSORT quality score ≥ 20 Exclusion: Did not compare Diazepam to non-IV Midazolam Animal studies Study design not randomized controlled or quasi-experimental Diazepam or Midazolam use for sedation or seizure prevention Setting: 6 randomized clinical trials, 5 pediatric ED, 1 residential facility, England (2), U.S (1), Israel (1), Iran (1), Uganda (1), Published 1997-2008
INTERVENTION	Midazolam by any non-intravenous route: Intranasal, intramuscular or buccal See Appendix for medication dosing used in the studies
CONTROL	Diazepam by intravenous or rectal route
OUTCOME	Primary Outcome: Seizure cessation Secondary Outcomes: Time to administration Time from administration to seizure cessation Respiratory complications
DESIGN	Systematic review and Meta-analysis: Randomized and non-randomized clinical trials

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review explicitly address a sensible clinical question?	Unclear. The 6 trials included in the primary analysis used varying doses and routes of antiepileptic medications, in both ED and non-ED settings, and varying definitions of both status epilepticus and seizure cessation. The question of the efficacy of Diazepam by “any route” compared to Midazolam by “any route” is broad. In addition, seizure definition and medication dosing varied between studies. The etiology of seizures was not presented. It would be difficulty to conclude that any specific route and dose was more efficacious for each of the medications without direct comparison of specific medications and routes.
Was the search for relevant studies detailed and exhaustive?	Yes. An exhaustive search included Pubmed, Web of knowledge, Embase, EBM reviews (Cochrane Database, Database of abstracts, Amer Col of Physicians Journal Club, Cochrane register of controlled trials), Cumulative Index to Nursing and Allied Health Literature, International Pharmaceutical Abstracts, Search of bibliographies of key articles and abstracts presented at conferences and of other key review articles. Search terms provided in appendix. Limited to English language only. A Funnel plot (Appendix B) and Begg’s test (p 0.07) demonstrated no statistically significant publication bias.
Was the risk of bias of the primary studies assessed?	Yes. Study inclusion required a CONSORT quality scale of ≥ 20 of a 30. The criteria included randomization, allocation concealment, repeatability of observations, and quality of writing.
Were the selection and assessment of studies reproducible?	Yes. Two independent reviewers assessed studies for inclusion. Disagreements were resolved by consensus. Kappa for inclusion was 0.95 indicating excellent inter-rater reliability. Inclusion criteria included assessment of study quality using the CONSORT quality scale and a randomized clinical trial checklist. Kappa for the quality assessment was not separately presented though the quality score was part of the inclusion criteria.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

See Forest Plots: Figures 2 & 3.
Not heterogeneous visually: confidence intervals overlap and comparable risk ratios.
Heterogeneity statistics: Cochran's Q test (p = 0.8) and I^2 statistic (I^2= 0%) indicate no statistically significant heterogeneity

WHAT ARE THE OVERALL RESULTS OF THE REVIEW?

N = 6 studies, 774 subjects

PRIMARY OUTCOME: FAILURE TO ACHIEVE SEIZURE CESSATION

MIDAZOLAM (ANY ROUTE) VERSUS DIAZEPAM (ANY ROUTE) (Figure 2, 6 trials)

	TREATMENT FAILURE	TREATMENT SUCCESS	
DIAZEPAM (IV, PR)	170	216	386
MIDAZOLAM (IM, IN, BUC)	112	276	388
	282	492	774

Risk of Failure Diazepam (Any Route): 170/386 = 44%
Risk of Failure Midazolam (Any Route): 112/388 = 29%
Risk Difference = Diazepam - Midazolam = 44– 29 = 15%, 95% CI (8.4, 21.8%)
Relative Risk = Diazepam/Midazolam = 44/29 = 1.52, 95% CI (1.27, 1.82),

PRIMARY OUTCOME: FAILURE TO ACHIEVE SEIZURE CESSATION

MIDAZOLAM (INTRAMUSCULAR, INTRANASAL) VS DIAZEPAM (INTRAVENOUS) (Figure3, 3 trials)

	TREATMENT FAILURE	TREATMENT SUCCESS	
DIAZEPAM (IV)	3	69	72
MIDAZOLAM (IM, IN)	4	70	74
	7	139	146

Risk of Failure Diazepam (Intravenous): 3/72 = 4.2%
Risk of Failure Midazolam (Intramuscular/Intranasal): 4/74 = 5.4%
Absolute Risk Difference = Diazepam – Midazolam = 4.2 – 5.4 = -1.2% (-6.8, 9.4%)
Relative Risk = Diazepam/Midazolam = 4.2/5.4 = 0.79, 95% CI (0.19, 3.26),

Midazolam (Buccal) vs Diazepam (PR):
Relative Risk: 1.54 (1.29, 1.85)

Time to Administration
Non-Intravenous Midazolam < Intravenous Diazepam
Mean Difference: 2.46 minutes, 95% CI (1.52, 3.39 minutes)

Time from Administration to Seizure Cessation
Non-Intravenous Midazolam > Intravenous Diazepam
Mean Difference: 0.68 minutes, 95% CI (-0.03, 1.39 minutes)

Respiratory Complications (Midazolam/Diazepam)
5/750 (0.76%) required intubation or ventilation
Relative Risk = 1.49, 95% CI (0.25, 8.72)

DID THE REVIEW ADDRESS CONFIDENCE IN EFFECT ESTIMATES?
See confidence intervals above

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were all patient-important outcomes considered?	Yes. Outcomes included ease of administration, cost, availability, potential for home use and pre-hospital use?
Are any postulated subgroup effects credible?	Sensitivity analyses did not reveal a change in results for dose, length of seizure required for inclusion or including partial versus generalized seizures.
What is the overall quality of the evidence?	Included 6 English-only studies. All studies had a CONSORT quality score of > 20 of 30 (range 23-28). No change in results if included studies with scores of 15-19 were added to the analysis. While there was no heterogeneity of study results though there was significant heterogeneity of study design.
Are the benefits worth the costs and potential risks?	Absolute risk difference = 44 - 29 = 15% Number needed to treat: NNT = 1/ARD = 1/0.15 = 7 You need to treat 7 patients with Midazolam by any route to prevent 1 additional treatment failure (lack of seizure cessation) when compared to Diazepam by any route. There were no clear adverse effects identified.

CLINICAL BOTTOM LINE

BACKGROUND: Status epilepticus is a common emergency department presentation. Delays in seizure cessation can lead to permanent neurologic injury. Obtaining intravenous access in a seizing child can be difficult to achieve. Non-intravenous epileptics could avoid the delay in seizure cessation due to delays in obtaining intravenous access. The optimal antiepileptic and route is unknown.

CLINICAL QUESTION: In children and young adults in status epilepticus is non-intravenous Midazolam superior to intravenous or rectal Diazepam as first line therapy for seizure cessation?

DESIGN/RISK OF BIAS: This was a meta-analysis of randomized clinical trials that included 6 studies and a total of 774 patients. This was a well-designed study. The authors performed an extensive search of the English language literature. Visual and statistical analysis did not identify publication bias. They utilized explicit inclusion and exclusion criteria. Inclusion criteria included an assessment of study quality with a CONSORT score of > 20 of 30 required for inclusion. Inter-rater reliability for study inclusion was excellent with a kappa of 0.95.

The 6 trials included in the primary analysis used varying doses and routes of antiepileptic medications, in both ED and non-ED settings, and varying definitions of both status epilepticus and seizure cessation. The etiology of seizures was not presented. The question of the efficacy of Diazepam by “any route” compared to Midazolam by “any route” is broad. It would be difficult to conclude that any specific route and dose was more efficacious for each of the medications without direct comparison of specific medications and routes.

PRIMARY RESULTS: There was a statistically significant 15% absolute risk reduction in failure rate with Midazolam by any route when compared to Diazepam by any route (Absolute Risk Difference (Diazepam - Midazolam) = 44– 29 = 15%, (-8.4, -21.8%,)). The number needed to treat was 7 (NNT = 1/ARD = 1/0.15 = 7). You need to treat 7 patients with Midazolam by any route to prevent 1 additional treatment failure (lack of seizure cessation) when compared to Diazepam by any route.

No difference was seen when comparing intramuscular and intranasal Midazolam to intravenous Diazepam (Absolute Risk Difference (Diazepam - Midazolam) = 4.2 – 5.4 = -1.2% (-6.8, 9.4%). The time to administration was shorter for Midazolam and though time from administration to seizure cessation was slightly longer for Midazolam, the overall time from drug ordered to seizure cessation was approximately 2 minutes shorter for Midazolam. There was no difference in the rate of respiratory depression.

APPLICABILITY: These results may be particularly applicable to parents and potentially by EMS for pre-hospital care and can be useful in the emergency department in a patient with difficult intravenous access.

AUTHOR’S CONCLUSION: “Published data support the efficacy and safety of non-intravenous routes of administration for midazolam, when compared to diazepam administered via any route in treating patients with status epilepticus, in the doses studied. Midazolam has characteristics that may make it an optimal choice for the treatment of seizing patients.”

POTENTIAL IMPACT: Non-intravenous routes of Midazolam should be considered if intravenous access cannot be obtained quickly. The limitation of combining disparate study methodologies should be considered when interpreting and applying the results of this study.

APPENDIX: STUDY'S MEDICATION DOSING

MEDICATION DOSING USED IN STUDIES		
DIAZEPAM	Intravenous	0.2 mg/kg or 0.3 mg/kg
	Rectal	0.5 mg/kg or 10 mg for age > 5 years
MIDAZOLAM	Intranasal	0.2 mg/kg
	Intramuscular	0.2 mg/kg
	Buccal	0.5 mg/kg or 10 mg for age > 5 years

STATUS EPILEPTICUS:
DIAZEPAM VS LORAZEPAM (PECARN)

In children (3 months-18years) presenting to
the emergency department in status epilepticus,
is Lorazepam superior to Diazepam
in the cessation of status epilepticus?

Katrina Knapp D.O., Martin Pusic M.D., PhD.
December 2014

Chamberlain JM, Okada P, Holsti M, Mahajan P, Brown KM, Vance C, Gonzalez V, Lichenstein R, Stanley R, Brousseau DC, Grubenhoff J, Zemek R, Johnson DW, Clemons TE, Baren J; Pediatric Emergency Care Applied Research Network (PECARN).

LORAZEPAM VS DIAZEPAM FOR
PEDIATRIC STATUS EPILEPTICUS

JAMA. 2014 Apr 23-30;311(16):1652-60.
PubMed ID: 24756515

STUDY DEFINITIONS	
POPULATION	Inclusion Children aged 3 months–18 years with generalized tonic-clonic status epilepticus defined as: 1. 3 or more convulsions within the preceding hour and currently experiencing a convulsion 2. 2 or more convulsions in succession with no recovery of consciousness and currently experiencing a convulsion, or 3. A current single convulsion of at least 5 minutes duration. Seizure could have started as a focal seizure, but to be included had to have loss of consciousness and generalized tonic-clonic seizures. Exclusion: Pregnancy, hypotension, significant cardiac dysrhythmia, need for emergent surgical intervention and general anesthesia, known contraindication to benzodiazepine, or benzodiazepine use within the preceding 7 days, including use of anticonvulsant medications by ambulance personnel. Setting: Multicenter network of U.S. Children's Hospitals (PECARN). 3/2008-3/2012
INTERVENTION	Diazepam: 0.2 mg/kg (max 8 mg)
CONTROL	Lorazepam: 0.1 mg.kg (max 4 mg)
CO-INTERVENTIONS	Seizure > 5 min: 2nd dose of the initial benzodiazepine at ½ the initial dose Seizure > 12 min: Fosphentoin/Phenytoin 15-20 mg/kg (Phenobarbital if allergic) Seizure > 20 min: Choice of antiepileptic at physician discretion (open label)
OUTCOME	Primary Efficacy Outcome: Cessation of status epilepticus by 10 minutes without recurrence within 30 minutes Primary Safety Outcome: Severe respiratory depression within 4 hours of initial medication, defined as the need for assisted ventilation (BVM or ET intubation) Secondary Outcomes: 1. Recurrence of seizure within 1 hour 2. Recurrence of seizure within 4 hours 3. Aspiration pneumonia 4. Incidence of sedation (using Riker score) 5. Requiring > 1 dose of study medication 6. Requiring only 1 dose of study medication 7. Requiring studying medication and additional anticonvulsant
DESIGN	Interventional: Randomized Control Trial

ARE THE RESULTS VALID?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Permuted block randomization (1:1) with a block size of 4 to receive either Lorazepam or Diazepam. Stratified by age group: 3 months to < 3 years, 3 years to < 13 years, 13 years to < 18 years
Was randomization concealed?	Allocation concealment not explicitly stated though it did not appear that there was a potential to bias allocation. Medication nurse or pharmacist (independent of the treating team) selected a vial of study medication sequentially based on the patients age group, and prepared it using a dosing card and based on the child's weight (Diazepam 0.2 mg/kg (Max 8 mg), Lorazepam 0.1 mg/kg (Max 4 mg)) Diluent was added to Lorazepam so final volumes of the medication were the same.
Were patients in the study groups similar with respect to known prognostic factors?	Yes (see Table 1 and Table 2). All 3 age groups had similar baseline characteristics with respect to gender, and ethnicity/race. None of the differences were statistically significant. There were no significant baseline differences of the distribution of the seizure etiologies between the treatment groups.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded	The authors state that the study was a double blinded. Opaque syringes were used to prevent visualization of the medication. The prepared medication was handed to the treating team. Study was blinded to the treating physician, but not stated if parents/ guardians were blinded. If the physician was blinded, the parents/ guardians were blinded as well. Unknown whether the pharmacist/nurse who was preparing the medication was blinded to which medication they were preparing. It is unlikely that if un-blinding occurred that it would influence the assessment of the study outcomes.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. All patients that were randomized in the per-protocol analysis had follow-up. Patients were followed up for adverse events for up to 24 hours or until discharge, whichever came first. A follow-up phone call was performed at 30 days to determine whether adverse events occurred after hospital discharge.
Were patients analyzed in the groups to which they were randomized?	Yes. An intention to treat analysis and a per-protocol analysis was performed on all randomized patients (See figure 1). Predefined protocol deviations included: study medication doses outside a margin of 30% desired dose, 2nd dose of medication given > 9 minutes after first dose, administering secondary anticonvulsant before 10 min, Benzodiazepines within 2 hours prior to enrollment, and intravenous extravasation (included 64 patients after randomization). Violations also included 15 patients who were systematically randomized incorrectly because of pharmacy error.
Was the trial stopped early	No. The trial was not stopped early.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

PRIMARY EFFICACY OUTCOME: SEIZURE CESSATION

	SEIZURE CESSATION*		
	Yes	No	
DIAZEPAM	101	39	140
LORAZEPAM	97	36	133

*within 10 min without return within 30 minutes

Absolute Risk Diazepam: 101/140 = 72.1%
Absolute Risk Lorazepam: 97/133 = 72.9%
Absolute Risk Difference: AR (L) – AR (D) = 0.8%, 95% CI (-11.4, 9.8%)

The investigators considered a 17% difference to be a clinically significant difference and conclude that Lorazepam was not superior to Diazepam.

Primary Safety Outcome: Need for assisted ventilation
Absolute Risk Diazepam: 26/162 = 16.0%
Absolute Risk Lorazepam: 26/148 = 17.6%
Absolute Risk Difference: AR (L) – AR (D) = 1.6%, 95% CI (-9.9, 6.8%)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Primary Outcomes:
Efficacy Risk Difference: 0.8% 95%CI (-11.4, 9.4%).
Safety Risk Difference: 1.6%, 95%CI (-9.9, 6.8%)
The confidence interval for both of the primary outcomes contain 0, so there is not a statistically significant difference.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Yes. The patients are similar to my patient population.
Were all clinically important outcomes considered?	The authors did not mention if any patients in either group had multiple seizure etiologies.
Are the likely treatment benefits worth the potential harm and costs?	The only benefit that was statistically significant in this study was the secondary outcome of the incidence of sedation. Patients who were treated with Lorazepam had a statistically significant increase in sedation. The primary safety outcome of assisted ventilation was not statistically significant between the two groups.

CLINICAL BOTTOM LINE

BACKGROUND: Rapid control of status epilepticus is desired to avoid permanent neuronal injury and acute life-threatening complications such as respiratory failure. Benzodiazepines are widely used as first line agents in stopping pediatric status epilepticus.

CLINICAL QUESTION: In children (3 months-18years) presenting to the emergency department in status epilepticus, is Lorazepam superior to Diazepam in cessation of status epilepticus?

DESIGN/VALIDITY: The study was a well-designed, double blinded, randomized control study that included 273 patients for 11 large academic pediatric hospitals in the United States in the PECARN Network in the primary analysis. There were no significant validity concerns in this study.

Prior studies have shown that Lorazepam was superior efficacy in terminating pediatric status epilepticus in the ED, had a longer duration of action, and lower incidence of respiratory depression. These studies had several limitations including: retrospective design, small sample size, single institution, and not having a standardized protocol of how quickly to administer the intravenous medication. In addition, this study excluded patients who had received benzodiazepines prior to entering the ED.

PRIMARY RESULTS: Lorazepam was not superior when compared to Diazepam in terminating pediatric status epilepticus in the ED at 10 minutes. The absolute risk difference between groups of 0.8%, 95%CI (-11.4, 9.8%). The investigators defined a 17% difference as clinically significant.

There was no significant difference in the need for assisted mechanical ventilation between the two groups. In the Diazepam group, 16% required assisted ventilation as compared to 17.6% in the Lorazepam group. The absolute risk difference was 1.6%, 95% CI (-9.9%, 6.8%).

Of the secondary outcomes, there was a significant difference between treatment groups in the incidence of sedation defined as a Riker scale < 3. The absolute risk difference was 16.9%, 95% CI (6.1, 27.7%). The number needed to harm is 6 (1/0.169). For every 6 patients treat with Lorazepam, 1 additional patient will be sedated compared to those treated with Diazepam.

APPLICABILITY: The results of this study appear to be applicable to patients who would meet the inclusion and exclusion criteria. Yet most patients who arrive in status epilepticus arrive via Emergency Medical Systems and have already received a benzodiazepine in route, so it makes it difficult to extrapolate to the majority of the population that is seen in our ED.

AUTHORS CONCLUSIONS: “Among pediatric patients with convulsive status epilepticus, treatment with Lorazepam did not result in improved efficacy or safety compared with Diazepam. These findings do not sup- port the preferential use of Lorazepam for this condition.”

POTENTIAL IMPACT: From an efficacy standpoint, approximately 60% in each group had seizure cessation within 5 minutes. An additional 30% required a second dose of the same benzodiazepine. Approximately 15% required Phenytoin or Fosphenytoin. From a safety standpoint, approximately 40% had some respiratory depression while 15% required assisted ventilation. This emphasizes that the need for a second line antiepileptic should be anticipated and that airway equipment and personal trained it its use should be rapidly available.

The results of this study indicate that Diazepam may be safely substituted for Lorazepam in pediatric patients in status epilepticus. This may be particularly helpful in the pre-hospital setting due to the requirement of refrigerating Lorazepam.

STATUS EPILEPTICUS:
KEPPRA VS PHENYTOIN (PERUKI)

In pediatric patients in convulsive status epilepticus unresponsive to first line therapy, is Levetiracetam superior to Phenytoin as a second line anticonvulsant in improving to time to seizure cessation?

Michael Mojica, M.D.
May, 2019

Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, Woolfall K, Roper L, Noblet J, Lee ED, Potter S, Tate P, Iyer A, Evans V, Appleton RE; Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI) collaborative.

LEVETIRACETAM VERSUS PHENYTOIN FOR SECOND-LINE TREATMENT OF PAEDIATRIC CONVULSIVE STATUS EPILEPTICUS (ECLIPSE): A MULTICENTRE OPEN-LABEL RANDOMISED TRIAL.

Lancet. 2019 Apr 17. pii: S0140-6736(19)30724-X.
PubMed ID: 31005385

STUDY DEFINITIONS	
POPULATION	Inclusion: 1. 6 months-18 years 2. Presenting with convulsive status epilepticus 3. Requiring second line antiepileptic treatment Exclusion: 1. Absence, myoclonic or non-convulsive status epilepticus or infantile spasms 2. Known or suspected to be pregnant 3. Contraindication or allergy to Phenytoin or Levetiracetam 4. Established renal failure 5. Received a second line antiepileptic before study screening 6. Previously enrolled in study 7. Convulsive status epilepticus ceased before study medication administration (could be included if seizures restarted) Setting: n=30 secondary or tertiary care center Emergency Departments (PERUKI Network: Paediatric Emergency Care Research in the United Kingdom and Ireland), 7/2015-4/2018
INTERVENTION	Levetiracetam: 40 mg/kg IV (maximum dose 2.5 grams) over 5 minutes
CONTROL	Phenytoin: 20 mg/kg IV (maximum dose 2.0 grams) over a minimum of 20 minutes (maximum infusion rate of 1mg/kg/min)
OUTCOME	Primary Outcome: Time from randomization to cessation of all visible signs of convulsive activity Subgroup analysis: weight (<12kg, 12-36kg, >36kg), sex, 1st time seizure Secondary Outcomes: 1. Required further antiepileptics after the initial treatment 2. Required rapid sequence intubation due to status epilepticus 3. Critical care admission 4. Serious adverse events: Death, Stevens-Johnson syndrome, rash, airway complications, cardiovascular instability, extravasation injury, agitation
DESIGN	Interventional: Randomized Clinical Trial (Superiority Hypothesis)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. A computer generated random sequence using permuted block sizes of 2 and four was supervised by an independent statistician. Randomization was stratified by study site.
Was randomization concealed?	Yes. Sites were provided with sequentially numbered, opaque, tamper proof enrollment packages. Use of the packs was monitored.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Treatment groups were similar in sex, age, weight, whether or not it was the 1st seizure, type of presenting seizure, seizure cause and maintenance antiepileptic (Table 1).
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Emergency department team members, participants, parents and statisticians were not blinded (open-label trial).
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	The study primary outcomes occurred during the patient's stay in the emergency department. Final follow-up was at 14 days after enrollment by chart review and a mailed questionnaire. Follow up data was reported for 96% (275/286) of patients (Table 3).
Were patients analyzed in the groups to which they were randomized?	Yes. The primary analysis was a modified intention to treat. This included all patients who were randomized and received the intended study medication. Those who were randomized but did not receive the study medication because seizures ceased prior to administration were excluded. The safety analysis include participants grouped by actual treatment received. 3 of the 152 patients in the Levetiracetam group received Phenytoin (Figure 1). 2 patients in the Phenytoin group did not receive the infusion due to loss of intravenous access
Was the trial stopped early?	No. The trial was monitored by an independent data and safety monitoring committee. The trial was not stopped early. Sample size determination required a total sample of 280 patients to detect a 15% improvement in seizure cessation. The final sample size was 286.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 286 (Levetiracetam: 152, Phenytoin: 134) in the modified intention to treat analysis.
Levetiracetam only: 132, Phenytoin only: 130, Both sequentially: 24 (17 L→P, 7 P→L)

PRIMARY OUTCOME: TIME TO SEIZURE CESSATION (MINUTES) (FIGURE 2)

ANALYSIS	PHENYTOIN	LEVETIRACETAM	HR[1] (95% CI)
Random → Start Infusion	12 min, IQR (8-17)	11 min, IQR (8-15)	Not provided
Random → Cessation	45 min, IQR (24, ?)	35 min, IQR (20,?)	1.20 (0.91, 1.60)
Start Infusion → Cessation	37 min, IQR (?)	24 min, IQR (?)	Not provided

RED = Not statistically significant, GREEN = Statistically significant
1. HR = Unadjusted Hazard Ratio (Phenytoin/Levetiracetam)

SECONDARY OUTCOMES (TABLE3)

ANALYSIS	PHENYTOIN	LEVETIRACETAM	RISK DIFFERENCE[1] (95% CI)
Cessation: Modified ITT[2]	64% (86/134)	70% (106/152)	5.6% (-5.3, 16.3%)
Need further AED ED	14.9% (20/134)	15.8% (24/152)	0.9% (-7.7, 9.2%)
Need further AED 24hr	12.7% (17/134)	9.2% (14/152)	-3.5% (-11.1, 3.8%)
Need RSI	35.1% (47/134)	30.0% (44/152)	-6.1% (-16.8, 4.6%)
Critical Care Admit	53.7% (72/134)	63.8% (97/152)	10.1% (-1.3, 21.2%)

RED = Not statistically significant, GREEN = Statistically significant
1. Risk Difference = Levetiracetam – Phenytoin (15% considered to be clinically significant)
2. Randomized & received study medication. Excluded sz cessation before study medication.
Phenytoin group: 2 patients discontinued treatment due to loss of IV access
Levetiracetam group: 3 patients received Phenytoin instead
Subgroup Analyses: No differences based on weight, sex, 1st time seizure

Adverse Events (Table 4):
Each individual adverse event < 10% prevalence
Most common: Agitation (Levetiracetam: 8%, Phenytoin: 3%)
No statistically significant difference: Either study medication alone or received both medications

Serious Adverse Events (n=5):
Phenytoin group: 3 in 2 patients: 2 in same patient, life-threatening hypotension and increased focal seizures and decreased consciousness (deemed related)
Levetiracetam group: 1 in 1 patient: Cardiac arrest due to obstructed ET tube (deemed unrelated)
Both study medications: 1 in 1 patient: Died of cerebral edema (deemed unrelated)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The confidence intervals for the hazard ratios and the risk differences are presented in the tables above. The confidence intervals for the risk differences are fairly wide.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Likely, yes. The inclusion of 30 secondary and tertiary center EDs in England and Ireland likely make the study's results generalizable to those meeting the study's inclusion and exclusion criteria in a variety of settings.
Were all patient important outcomes considered?	Yes. The study included a number of efficacy and safety outcomes in the ED, during admission and at follow-up. The sample size is inadequate to assess the likelihood of rare adverse events such as Stevens-Johnson syndrome.
Are the likely treatment benefits worth the potential harm and costs?	Unclear. There were no statistically significant differences between the 2 study groups in any of the study's efficacy or safety outcomes.

CLINICAL BOTTOM LINE

BACKGROUND: Status epilepticus is associated with significant morbidity and mortality. The longer the duration, the greater the risk for adverse outcomes. Benzodiazepines are recommended as first line agents but their efficacy is approximately 50%. The most commonly recommended second line agents are Phenytoin and Fosphenytoin. Their use is associated with an efficacy of approximately 50%. In addition, their use is associated with significant adverse events such as hepatotoxicity, pancytopenia, Stevens-Johnson syndrome, hypotension, arrhythmias and extravasation injury. Levetiracetam (Keppra) had been proven efficacious in small case series, can be administered more rapidly (5 minutes vs 20 minutes) and has fever adverse reaction and drug interactions when compared to Phenytoin.

CLINICAL QUESTION: In pediatric patients in convulsive status epilepticus unresponsive to first line therapy, is Levetiracetam superior to Phenytoin as a second line anticonvulsant in improving to time to seizure cessation?

DESIGN/VALIDITY: This was a well-designed randomized clinical trial enrolling patients at 30 secondary and tertiary care Emergency Departments in England and Ireland (PERIUKI Network). Children in status epilepticus requiring second line antiepileptics were randomized to receive Phenytoin: 20 mg/kg IV/IO (maximum dose 2 grams) over a minimum of 20 minutes or Levetiracetam: 40 mg/kg IV/IO (maximum dose 2.5 grams) over 5 minutes. Allocation was concealed. Parents, guardians, treating physicians, research nurses and the investigators were <u>not</u> blinded to the treatment group. Patients receiving the study medication as baseline antiepileptic therapy were not excluded and Levetiracetam was the most common baseline medication.

The primary outcome was time from randomization to cessation of all visible signs of convulsive activity. Treatment groups were similar in sex, age, weight, whether or not it was the first seizure, type of presenting seizure, seizure cause and maintenance antiepileptic (Table 1).

PRIMARY RESULTS: 286 patients were included in the study's modified intention-to-treat analysis. (Levetiracetam: 152, Phenytoin: 134). The modified intention to treat analysis included all patients who were randomized and received the intended study medication and excluded those who were randomized but did not receive the study medication because seizures ceased prior to their administration. 3 patients in the Levetiracetam group received Phenytoin instead. 2 patients in the Phenytoin group did not receive the infusion due to loss of IV access. 8.4% of patients received both study medications.

There was no statistically significant difference between the two groups in the study's primary outcome of time from randomization to cessation of all visible signs of convulsive activity (Phenytoin: 45 min, IQR (24, ?), Levetiracetam: 35 min, IQR (20,?), unadjusted Hazard Ratio (P/L): 1.20, 95% CI (0.91, 1.60). The time from the completion of the study medication infusion until seizure cessation was not provided. This is important because the during of the infusion was difference for the two medications (Levetiracetam: 5 minutes, Phenytoin: minimum of 20 minutes).

PRIMARY OUTCOME: TIME TO SEIZURE CESSATION (MINUTES) (FIGURE2)			
ANALYSIS	PHENYTOIN	LEVETIRACETAM	HR[1] (95% CI)
Random → Start Infusion	12 min, IQR (8-17)	11 min, IQR (8-15)	Not provided
Random → Cessation	45 min, IQR (24, ?)	35 min, IQR (20,?)	1.20 (0.91, 1.60)
Start Infusion → Cessation	37 min, IQR (?)	24 min, IQR (?)	Not provided
RED = Not statistically significant, GREEN = Statistically significant 1. HR = Unadjusted Hazard Ratio (Phenytoin/Levetiracetam)			

There was no statistically significant difference between the study groups in the proportion with seizure cessation (Levetiracetam: 70% (106/152), Phenytoin: 64% (86/134), Risk Difference: 5.6%, 95 CI (-5.3, 16.3%)). The authors considered a 15% difference to be clinically significant in their sample size determination. There was no statistically significant difference between the study groups in the need for further antiepileptic therapy in the ED or within the first 24 hours, need for rapid sequence intubation or the proportion admitted to a critical care setting (Table below).

SECONDARY OUTCOMES (TABLE3)			
ANALYSIS	PHENYTOIN	LEVETIRACETAM	RISK DIFFERENCE[1] (95% CI)
Cessation: Modified ITT[2]	64% (86/134)	70% (106/152)	5.6% (-5.3, 16.3%)
Need further AED ED	14.9% (20/134)	15.8% (24/152)	0.9% (-7.7, 9.2%)
Need further AED 24hr	12.7% (17/134)	9.2% (14/152)	-3.5% (-11.1, 3.8%)
Need RSI	35.1% (47/134)	30.0% (44/152)	-6.1% (-16.8, 4.6%)
Critical Care Admit	53.7% (72/134)	63.8% (97/152)	10.1% (-1.3, 21.2%)
RED = Not statistically significant, GREEN = Statistically significant 1. Risk Difference = Levetiracetam – Phenytoin (15% considered to be clinically significant) 2. Randomized & received study medication. Excluded sz cessation before study medication. Phenytoin group: 2 patients discontinued treatment due to loss of IV access Levetiracetam group: 3 patients received Phenytoin instead Subgroup Analyses: No differences based on weight, sex, 1st time seizure			

There was no statistically significant difference in the rate of adverse events between either study medication alone or those who received both medications. The most common adverse event was agitation (Levetiracetam: 8%, Phenytoin: 3%). 2 severe adverse events thought to be related to the study medication occurred in a single patient receiving Phenytoin. The sample size is inadequate to assess the likelihood of rare adverse events such as Stevens-Johnson syndrome.

APPLICABILITY: The inclusion of 30 secondary and tertiary center EDs in England and Ireland likely make the study's results generalizable to those meeting the study's inclusion and exclusion criteria in a variety of settings.

AUTHOR'S CONCLUSION: "The EcLiPSE trial did not show that levetiracetam was superior to phenytoin in cessation rate of convulsive status epilepticus, the time taken to terminate convulsive status epilepticus, or adverse reactions and events. However, the results, together with previously reported safety profiles and relative ease of administration of levetiracetam, suggest that it could be an appropriate alternative to phenytoin as the first-choice anticonvulsant for second-line treatment of paediatric convulsive status epilepticus".

POTENTIAL IMPACT: Levetiracetam was found to not superior to Phenytoin in the time from randomization to seizure cessation or the proportion of patients with cessation of seizures. Phenytoin is associated with a number of serious adverse events. Levetiracetam does not need to be superior to Phenytoin in terms of efficacy to provide a safe alternative to Phenytoin. Levetiracetam offers the additional benefit as a medication for status epilepticus in that it is more commonly transitioned to be the patient's maintenance antiepileptic. The use of Fosphenytoin compared to Phenytoin could possibly reduce adverse events and eliminate Levetiracetam's time of infusion benefit but at increased monetary cost.

It is important to acknowledge that 32% of patients in the study required rapid sequence intubation. This makes it essential to anticipate the need for addition antiepileptic medications and prepare equipment and medications for rapid sequence intubation.

See also:

Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, Francis KL, Sharpe C, Harvey AS, Davidson A, Craig S, Phillips N, George S, Rao A, Cheng N, Zhang M, Kochar A, Brabyn C, Oakley E, Babl FE; PREDICT Research Network.
Levetiracetam versus Phenytoin for Second-Line Treatment of Convulsive Status Epilepticus in Children (ConSEPT): An Open-Label, Multicentre, Randomised Trial.
Lancet. 2019 Apr 17. pii: S0140-6736(19)30722-6., PubMed ID: 31005386

LINK: PEMCAR IBOOK LINK TO ABOVE STUDY'S REVIEW

STATUS EPILEPTICUS: KEPPRA VS PHENYTOIN (PREDICT)

In pediatric patients in convulsive status epilepticus unresponsive to first line therapy with 2 doses of a benzodiazepine, is Levetiracetam superior to Phenytoin as a second line anticonvulsant in improving the rate of seizure cessation 5 minutes after the study drug infusion is completed?

Michael Mojica, M.D.
May, 2019

Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, Francis KL, Sharpe C, Harvey AS, Davidson A, Craig S, Phillips N, George S, Rao A, Cheng N, Zhang M, Kochar A, Brabyn C, Oakley E, Babl FE; PREDICT Research Network.

LEVETIRACETAM VERSUS PHENYTOIN FOR SECOND-LINE TREATMENT OF CONVULSIVE STATUS EPILEPTICUS IN CHILDREN (CONSEPT): AN OPEN-LABEL, MULTICENTRE, RANDOMISED TRIAL.

Lancet. 2019 Apr 17. pii: S0140-6736(19)30722-6.
PubMed ID: 31005386

STUDY DEFINITIONS	
POPULATION	Inclusion: 1. 3 month-6 years 2. Status epilepticus: International League Against Epilepsy definition a. Unresponsive with continued movements (tonic, jerky) > 5 minutes b. ≥ 2 recurrent seizures without a recovery of consciousness between c. ≥ 3 seizures in the past hour with current seizure 3. Unresponsive to 2 doses of a Benzodiazepine Exclusion: 1. Previously enrolled in study 2. On Levetiracetam or Phenytoin at baseline 3. Levetiracetam, Phenytoin, Phenobarbitone or Paraldehyde in the past 24 hrs 4. History of seizures refractory to Phenytoin 5. Allergy to study drugs 6. Status Epilepticus due to major trauma or eclampsia Setting: PREDICT Network (Australia, New Zealand), n = 13 (8 Children's, 5 General Hospitals), 3/2015-11/2017
INTERVENTION	Levetiracetam: 40 mg/kg IV/IO (maximum dose 3 grams) over 5 minutes (100 mg/ml concentration diluted 1:1 in normal saline (minimum 10 milliliters))
CONTROL	Phenytoin: 20 mg/kg IV/IO (maximum dose 1 gram) over 20 minutes (50 mg/ml concentration diluted 1:4 in normal saline (minimum 20 milliliters))
CO-INTERVENTIONS	First line therapy with 2 doses of a Benzodiazepine (Midazolam: 94%) At 5 minutes after completion of the infusion, if seizure activity continued the patient received the alternative study drug. RSI recommended by local protocols if refractory to initial study medication
OUTCOME	Primary Outcome: Seizure cessation 5 minutes after end of study drug infusion completed: 10 minutes after starting Levetiracetam Infusion (5-minute infusion) 25 minutes after starting Phenytoin infusion (20-minute infusion) Video, if available (67%) was reviewed (2 EM, 1 Neuro) blinded to study group Subgroup Analyses: Age (5 years, > 5 years), focal vs generalized, febrile vs afebrile, 1st line Benzodiazepine (Midazolam vs Other). Secondary Outcomes: 1. Seizure cessation at 2 hours after start of infusion without the need for: a. Further seizure management b. RSI or further seizure management with the exception of the 2nd study agent if the first was not successful 2. Need for RSI for seizure management 3. Time to seizure cessation 4. ICU admission 5. Serious adverse events: Death, serious unexpected airway complication in the first 24 hours, cardiovascular instability (arrest, arrythmias requiring defibrillation, other life-threatening events 6. Length of stay: Inpatient, ICU 7. Seizure status: Earlier of 1 mo after discharge or 2 mo after study entry 8. Safety outcomes: Death, manual airway repositioning, oral or nasal airway placement, positive pressure ventilation, tracheal intubation, fluid bolus, cardiac chest compressions, cardiac defibrillation, allergic reaction, extravasation of intravenous or intraosseous infusions, purple glove syndrome, and any other adverse event reported by clinical staff.
DESIGN	Interventional: Randomized Clinical Trial (Superiority hypothesis)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized by computer in permuted blocks. An independent statistician prepared the allocation sequence. Randomization was stratified by study site and age (5 years, > 5 years).
Was randomization concealed?	Yes. An independent pharmacist prepared identical, sealed, opaque envelopes. Patients were allocated based on the next numbered envelope for the appropriate age group.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Treatment groups were similar in demographic characteristics, medical history, seizure type, type and route of initial benzodiazepine received as first line therapy and clinical management prior to the administration of the study medication (Table 1).
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Parents, guardians, treating physicians, research nurses and the investigators were not blinded to the study group.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. The primary outcome was assessed at the time of emergency department care. The research nurse obtained additional information during the initial hospitalization and by phone follow at 1 month. Phone follow up was available for 86% (200/233) of the patients and was similar in both groups.
Were patients analyzed in the groups to which they were randomized?	Yes. The primary analysis was an intention to treat analysis. A per protocol analysis was also performed excluding patients undergoing RSI and intubation between randomization and start of the first study medication. A modified intention-to-treat analysis was also performed excluding patients undergoing RSI and intubation between randomization and start of the first study medication and patients with seizure cessation between randomization and the start of the study drug.
Was the trial stopped early?	No. The trial was not stopped early. The sample size determination required 91 patient per study group (total 182) to determine a difference (effect size) of 20%. 233 patients were included in the primary intention-to-treat analysis.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 233
First line AED: Midazolam 94%
Median time before infusion of the 1st study medication: 73 minutes

PRIMARY OUTCOME: SEIZURE CESSATION 5 MINUTES AFTER INFUSION: TABLE2

ANALYSIS	PHENYTOIN	LEVETIRACETAM	RISK DIFFERENCE (95% CI)
Intention to Treat	60% (68/114)	50% (60/119)	-9.2 (-21.9, 3.5%)
Modified ITT[1]	55% (53/96)	46% (46/101)	-9.7 (-23.6, 4.2%)
Per Protocol[2]	60% (67/111)	50% (59/117)	-9.9 (-22.8, 2.9%)

RED = Not statistically significant, GREEN = Statistically significant
1. Excluding 5 patients intubated and 31 patients whose seizure stopped before 1st study drug
2. Excluding 5 patients intubated before 1st study drug
Subgroup Analyses: No difference based on age, focal vs generalized seizure, febrile vs afebrile presentation and 1st line Benzodiazepine used (Midazolam vs Other)
Video confirmation: Available 67%, 4.5% (7/235) disagreement, no difference is primary outcome

SECONDARY OUTCOMES: EFFICACY

	PHENYTOIN	LEVETIRACETAM	RISK DIFF (95% CI)
2hrs: Cessation after 1st AED	54% (62/114)	51% (61/119)	-3.1% (-15.9, 9.7%)
2hrs: Cessation after 2nd AED[1]	24% (27/114)	21% (25/119)	-2.7 (-13.4, 8%)
2hrs: Cessation after 1st or 2nd AED	78% (89/114)	72% (86/119)	-5.8 (-16.9, 5.3%)
Start 1st AED → Termination (min)	22 (IQR 9-49m)	17 (IQR 5-30m)	-5.0 (-13.5, 3.5min)

RED = Not statistically significant, GREEN = Statistically significant
1. Proportion responding to 2nd AED: Phenytoin: 64% (27/42). Levetiracetam: 52% (25/48)

Secondary Outcomes: Adverse Events: No statistically significant difference in:
1. Rate of rapid sequence intubation, rate of ICU admission or length of stay in hospital or ICU
2. Serious adverse events within 2 hours of study medication or during admission (Table 4)
3. Follow-up rate of recurrent seizures or status epilepticus, rate of AED use (Table 5)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence intervals for the risk differences for the primary and secondary outcomes are included in the above tables. The confidence intervals are fairly wide.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Likely, yes. The inclusion of 13 centers that are both children's hospitals and general hospitals in Australia and New Zealand likely make the study's results generalizable to those meeting the study's inclusion and exclusion criteria in a variety of settings. The influence of the inclusion of ethnic groups not typical of the U.S. is unclear but there is no reason to believe that this would influence the study's outcomes. Patient on Levetiracetam or Phenytoin at baseline were excluded so they study results are not applicable to them.
Were all patient important outcomes considered?	Yes. The study included a number of efficacy and safety outcomes in the ED, during admission and at follow-up. The sample size is inadequate to assess the likelihood of rare adverse events such as Stevens-Johnson syndrome.
Are the likely treatment benefits worth the potential harm and costs?	Unclear. There were no statistically significant differences between the 2 study groups in any of the study's efficacy or safety outcomes. However, it is unclear, why the authors utilized a superiority hypothesis rather than an equivalence or non-inferiority hypothesis. As the authors state in their introduction, Phenytoin is associated with a number of serious adverse events. Levetiracetam does not need to be superior to Phenytoin in terms of efficacy to provide a safe alternative to Phenytoin.

CLINICAL BOTTOM LINE

BACKGROUND: Status epilepticus is associated with significant morbidity and mortality. The longer the duration, the greater the risk for adverse outcomes. Benzodiazepines are recommended as first line agents but their efficacy is approximately 50%. The most commonly recommended second line agents are Phenytoin and Fosphenytoin. Their use is associated with an efficacy of approximately 50%. In addition, their use is associated with significant adverse events such as hepatotoxicity, pancytopenia, Stevens-Johnson syndrome, hypotension, arrhythmias and extravasation injury. Levetiracetam (Keppra) had been proven efficacious in small case series, can be administered more rapidly (5 minutes vs 20 minutes) and has the potential fo rfever adverse reaction and drug interactions when compared to Phenytoin and Fosphenytoin.

CLINICAL QUESTION: In pediatric patients in convulsive status epilepticus unresponsive to first line therapy with 2 doses of a benzodiazepine, is Levetiracetam superior to Phenytoin as a second line anticonvulsant in improving the rate of seizure cessation 5 minutes after study drug infusion is completed?

DESIGN/VALIDITY: This was a well-designed randomized clinical trial enrolling patient at 13 Children's and general hospitals in Australia and New Zealand (PREDICT Network). Children in status epilepticus who were not responsive to at least two doses of a Benzodiazepine were included. Patients were randomized to receive Phenytoin: 20 mg/kg IV/IO (maximum dose 1 gram) over 20 minutes or Levetiracetam: 40 mg/kg IV/IO (maximum dose 3 grams) over 5 minutes. If seizure cessation did not occur within 5 minutes of the completion of the study infusion, the alternative study drug was administered. Allocation was concealed. Parents, guardians, treating physicians and research nurses were not blinded to the allocation group.

The primary outcome was seizure cessation 5 minutes after the completion of study drug infusion (10 minutes after starting Levetiracetam Infusion and 25 minutes after starting Phenytoin infusion). A number of both safety and efficacy secondary outcomes were assessed. Treatment groups were similar with regard to demographic characteristics, medical history, seizure type, type and route of initial benzodiazepine received as first line therapy and clinical management prior to the administration of the study medication (Table 1).

PRIMARY RESULTS: In the primary intention to treat analysis, there was not a statistically significant difference between the two study medication in the primary outcome of seizure cessation 5 minutes after the completion of the study medication infusion (Phenytoin: 60% (68/114), Levetiracetam: 50% (60/119), Risk Difference: -9.2, 95% CI (-21.9, 3.5)). This difference is also considered not clinically significant by the authors criteria of a 20% improvement in seizure cessation for Levetiracetam to be considered superior to Phenytoin. The results were similar in the modified intention to treat and the per protocol analysis. There was no difference in the primary outcome in the subgroup analyses based on age, focal vs generalized seizure, febrile vs afebrile seizure and 1st line Benzodiazepine used.

PRIMARY OUTCOME: SEIZURE CESSATION 5 MINUTES AFTER INFUSION: TABLE 2			
ANALYSIS	PHENYTOIN	LEVETIRACETAM	RISK DIFFERENCE (95% CI)
Intention to Treat	60% (68/114)	50% (60/119)	-9.2 (-21.9, 3.5%)
Modified ITT[1]	55% (53/96)	46% (46/101)	-9.7 (-23.6, 4.2%)
Per Protocol[2]	60% (67/111)	50% ((59/117)	-9.9 (-22.8, 2.9%)
1. Excluding 5 patients intubated and 31 patients whose seizure stopped before 1st study drug 2. Excluding 5 patients intubated before 1st study drug Subgroup Analyses: No difference based on age, focal vs generalized seizure, febrile vs afebrile presentation and 1st line Benzodiazepine used (Midazolam vs Other) Video confirmation: Available 67%, 4.5% (7/155) disagreement, no difference is primary outcome RED = Not statistically significant, GREEN = Statistically significant			

Of the patients who did not respond to the first study medication, an additional 22% responded to the alternative AED ((Phenytoin: 24% (27/114), Levetiracetam: 21% (25/119)). This could potentially half the rapid sequence intubation rate in those that did not respond to the first study medication). The cessation rate after responding to the first or second AED was approximately 75% ((Phenytoin: 78% (89/114), Levetiracetam: 72% (86/119)).

There was no statistically significant difference between the two study medications in any of the secondary safety outcomes analyzed. The sample size is inadequate to assess the likelihood of rare adverse events such as Steven's Johnson Syndrome.

APPLICABILITY: The inclusion of 13 centers that are both children's hospitals and general hospitals in Australia and New Zealand likely make the study's results generalizable to those meeting the study's inclusion and exclusion criteria in a variety of settings. The influence of the inclusion of ethnic groups not typical of the U.S. is unclear but there is no reason to believe that this would influence the study's outcomes. Patient on Levetiracetam or Phenytoin at baseline were excluded so they study results are not applicable to them. An average of 73 minutes elapsed prior to the first study medication. This may not be similar to urban population with shorter transport times and may underestimate the efficacy of the study medications as later treatment is associated with poorer efficacy.

AUTHOR'S CONCLUSION: "In conclusion, we found that levetiracetam is not superior to phenytoin for treatment of children with convulsive status epilepticus with continued clinical seizure activity after treatment with benzodiazepines. Although both drugs were associated with considerable failure rates when given by themselves, treatment with one drug and then the other reduced the failure rate by more than 50%, at the expense of only an additional 10 minutes (compared with giving phenytoin alone). Clinicians should therefore consider sequential use of phenytoin and levetiracetam, or levetiracetam and phenytoin, for management of paediatric convulsive status epilepticus before moving on to RSI and intubation."

POTENTIAL IMPACT: In the intention to treat analysis, Levetiracetam (50%) was found not be not superior to Phenytoin (60%) (Risk Difference: -9.2, 95% CI (-21.9, 3.5)). However, it is unclear, why the authors utilized a superiority hypothesis rather than an equivalence or non-inferiority hypothesis. As the authors state in the introduction, Phenytoin is associated with a number of serious adverse events. Levetiracetam does not need to be superior to Phenytoin in terms of efficacy to provide a safe alternative to Phenytoin. The use of Fosphenytoin compared to Phenytoin could possibly reduce adverse events and eliminate Levetiracetam's time of infusion benefit but at increased monetary cost.

Of the patients who did not respond to the first study medication, an additional 22% responded to the alternative AED ((Phenytoin: 24% (27/114), Levetiracetam: 21% (25/119)). The use of both study medication in sequence could potentially half the rapid sequence intubation rate in those that did not respond to the 1st study medication.

It is important to acknowledge that approximately 50% of the patients were still seizing after the first study drug and 25% after the second alternative study drug. This makes it essential to anticipate the need for addition antiepileptic medications and prepare equipment and medications for rapid sequence intubation.

See also

Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, Woolfall K, Roper L, Noblet J, Lee ED, Potter S, Tate P, Iyer A, Evans V, Appleton RE;
Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI) collaborative.
Levetiracetam Versus Phenytoin For Second-Line Treatment Of Paediatric Convulsive Status Epilepticus (EcLiPSE): A Multicentre, Open-Label, Randomised Trial.
Lancet. 2019 Apr 17. pii: S0140-6736(19)30724-X., PubMed ID: 31005385

LINK: PEMCAR IBOOK LINK TO ABOVE STUDY'S REVIEW

STATUS EPILEPTICUS: PREHOSPITAL MIDAZOLAM VS LORAZEPAM

In children and adult patients in status epilepticus in the prehospital setting, is intramuscular Midazolam at least as effective (Non-Inferior) as intravenous Lorazepam for terminating seizures prior to emergency department arrival?

Joanne Agnant, M.D., Michael Tunik, M.D.
March 2012

Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, Barsan W; NETT Investigators.

INTRAMUSCULAR VERSUS INTRAVENOUS THERAPY FOR PREHOSPITAL STATUS EPILEPTICUS. (RAMPART: RAPID ANTICONVULSANT MEDICATIONS PRIOR TO ARRIVAL TRIAL)

N Engl J Med. 2012 Feb 16;366(7):591-600.
PubMed ID: 22335736

STUDY DEFINITIONS	
POPULATION	Inclusion: Children estimated ≥ 13 kg and adults requiring benzodiazepines for status epilepticus in prehospital setting. Status epilepticus defined as a seizure > 5 minutes by witness or repeat seizure without return to baseline. Exclusion: Seizures related to major trauma, hypoglycemia, cardiac arrest, or a heart rate of less than 40 beats per minute, known allergy to Midazolam or Lorazepam, pregnant or a prisoner, treated as part of another study or, preemptively opted out of by wearing a medical-alert tag “RAMPART declined.” Setting: Multicenter, Neurological Emergencies Treatment Trials (NETT) network: 4314 paramedics, 33 EMS agencies, and 79 receiving hospitals across the U.S., 6/2009-1/2011
INTERVENTION	Intramuscular Midazolam: Via auto-injector: 5 mg (13-40 kg), 10 mg (> 40 kg) Followed by intravenous Placebo
CONTROL	Intravenous Lorazepam: 2 mg (13-40 kg), 4 mg (> 40 kg) Followed by intramuscular Placebo via auto-injector
CO-INTERVENTIONS	If difficult to obtain intravenous access, paramedics instructed to continue attempts for at least 10 minutes, permitted to use intraosseous access Rescue therapy, as per local EMS protocol if still convulsing 10 minutes after last study medication was administered.
OUTCOME	Primary Outcome: Termination of seizures before arrival in the emergency department without the need for rescue therapy. Secondary Outcomes: 1. Time from study-box opening to termination of convulsions 2. Time from initiation of active-drug administration to seizure termination 3. Frequency, duration of hospitalization, admissions to the intensive care unit 4. Frequencies of acute endotracheal intubation, acute seizure recurrence. 5. Serious adverse events
DESIGN	Interventional: Randomized clinical trial (non-inferiority hypothesis)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Authors report simple randomization by pharmacy with equal number of subjects assigned to the two study groups.
Was randomization concealed?	Yes. A double-dummy strategy was used. In this strategy, both treatment groups received both placebo and active drug. In this study, each kit was randomly assigned by the pharmacy with either intramuscular drug and intravenous placebo or intramuscular placebo and active intravenous drug
Were patients in the study groups similar with respect to known prognostic factors?	Yes (Table 1). The two study groups appeared to be similar with respect to age, medication dose, history of epilepsy, final diagnosis, and precipitating cause. There were more males in the Midazolam group. There were also slightly more whites in the Lorazepam group. These two differences do not appear to result in any significant bias.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The paramedics were blinded to which treatment strategy the patient was allocated.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes (Figure 1). Follow up was complete at arrival to the ED (time of primary outcome measurement). It was not mentioned if they were able to get complete follow up with respect to the secondary outcomes (i.e. duration of hospitalization). The length of stay in ICU patients was reported for 278 of 289 (96%) and length of stay on the ward was reported for 536 of 550 (97%).
Were patients analyzed in the groups to which they were randomized?	Yes (Figure 1). The patients were analyzed in the groups to which they were randomized, using an intention to treat analysis. They were also analyzed in the medication groups to which they actually received in a per protocol analysis.
Was the trial stopped early	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

SEIZURE ABSENCE WITHOUT RESCUE THERAPY ON ED ARRIVAL (ITT ANALYSIS)

	SEIZURE ABSENT	SEIZURE PRESENT	
INTRAVENOUS LORAZEPAM	282	163	445
INTRAMUSCULAR MIDAZOLAM	329	119	448

Primary Outcome
Absolute Risk IM Midazolam: 329/448 (73.4%)
Absolute Risk IV Lorazepam: 282 /445 (63.4%)
Absolute Risk Difference: 73% - 63% = 10%, 95% CI (4, 16%)
Relative Risk = (Midazolam)/(Lorazepam) = 73/63 = 1.16, 95% CI (1.06, 1.27).

Results were similar in the per protocol analysis

Secondary Outcomes

Time until drug given: IM (1.2 minutes) < IV (4.8 minutes)
Time drug given to seizure end: IM (3.3 minutes) > IV (1.6 minutes)
Time from start of protocol to seizure end: IM = IV

Admission:
Midazolam: 57.6%, Lorazepam: 65.6%,
Relative Risk: 0.88, 95% CI (0.79, 0.98)

Frequency of ET intubation, recurrent seizures and other safety outcomes were similar in each group.

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See above for confidence intervals for the absolute risk difference and relative risk for the primary outcome. The authors considered Midazolam non-inferior to Lorazepam if the lower limit of the confidence interval for the absolute risk difference was not less than 10% less for Midazolam. The results were statistically non-inferior and superior for Midazolam

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. Race and ethnicity not as out populations. The results do not apply to children < 13 kg.
Were all patient important outcomes considered?	No. Importantly, transport times to the ED were not reported. A longer duration of transit in one group would allow for a longer time of seizure cessation before ED arrival and would biased the results in favor of that group. The authors also did not present: hypoxemia, length of sedation or length of stay in the ED. It was had been helpful to present a mg/kg amount of anticonvulsant received. This would be important in the group of those 13-40 kg. At 5 mg of Midazolam that group could have received 0.15 mg/kg – 0.4 mg/kg. At 2 mg of Lorazepam that group could have received 0.05 mg/kg – 0.15 mg/kg.
Are the likely treatment benefits worth the potential harm and costs?	NNT (Number needed to treat) = 1/ARD = 1/0.1 = 10 (95% CI 6-25). Ten patients would need to be treated with IM Midazolam to prevent 1 additional patient from arriving in the ED actively seizing when compared to Lorazepam. Other benefits to midazolam include not having to place an intravenous line, which would be safer for EMS personnel and not requiring refrigeration as required for Lorazepam.

CLINICAL BOTTOM LINE

BACKGROUND: The ideal antiepileptic regimen to control prehospital seizures has not been established. Intravenous Lorazepam has been proven efficacious but obtaining an intravenous line in the prehospital setting is often difficult and increases the time to drug delivery. Intramuscular Lorazepam has a longer time to onset then intramuscular Midazolam. Midazolam has been shown to be efficacious via multiple routes (intramuscular, intranasal, buccal) but has a longer duration of onset then intravenous Lorazepam.

CLINICAL QUESTION: In children and adult patients in status epilepticus in the prehospital setting is intramuscular Midazolam at least as effective (non-Inferior) as intravenous Lorazepam for terminating seizures prior to emergency department arrival?

DESIGN/VALIDITY: This was a well-designed, multicenter, randomized clinical trial to determine if intramuscular Midazolam was non-inferior to intravenous Lorazepam in patients with status epilepticus in the prehospital setting. It included 893 patients in the primary intention to treat analysis.

It would have been helpful if ambulance transport times were compared between the study groups. A longer transit time would allow for a longer period for seizures to cease and bias the results of the study toward the group with the longer transit time.

Finally, because standard dosing was used it would have been helpful to see response based on mg/kg doses in the 13-40 kg subgroups. At 5 mg of Midazolam the 13-40 kg group could have received 0.15 mg/kg – 0.4 mg/kg. At 2 mg of Lorazepam the 13-40 kg group could have received 0.05 mg/kg – 0.15 mg/kg.

PRIMARY RESULTS: Midazolam delivered by auto-injector, given to patients seizing for > 5 min by paramedics, resulted in 10% (M 73.4% vs L 63.4) fewer patients who were still seizing on arrival to the ED. Though designed to determine that Midazolam was not inferior to Lorazepam it the rules were also statistically significant when analyzed as a superiority hypothesis. Though 10% of the Lorazepam group did not receive the study medication in the intention to treat analysis the results were the same in the per protocol analyses. There was no difference from the time of the start of the protocol until seizure cessation. Those treated with intramuscular Midazolam had a higher rate of discharge from the emergency department and had similar or lower rates of recurrent seizures and endotracheal intubation. There were no differences in complication rates including ICU admission, recurrent seizure, need for intubation, or hospital length of stay.

APPLICABILITY: The use of 33 emergency medical services in the U.S. likely makes this study's results generalizable to those with status epilepticus who do not meet study exclusion criteria. This data is not generalization to the infant/toddler less than 13 kg. The use of an auto-injector for medication dosing is not the standard of care and will need to be addressed before implementing a change in strategy

AUTHOR'S CONCLUSION: "In conclusion, intramuscular Midazolam is non-inferior to intravenous Lorazepam in stopping seizures before arrival in the emergency department in patients with status epilepticus treated by paramedics. Intramuscular Midazolam is also as safe as intravenous Lorazepam. The group of subjects treated with intramuscular Midazolam had a higher rate of discharge from the emergency department than the group treated with intravenous Lorazepam and had similar or lower rates of recurrent seizures and endotracheal intubation. The intramuscular administration of midazolam by EMS is a practical, safe, and effective alternative to the intravenous route for treating prolonged convulsive seizures in the prehospital setting."

POTENTIAL IMPACT: This study will serve to support the practice of using intramuscular Midazolam in the patient in status epilepticus in the prehospital setting. The use of an auto-injector for medication dosing is not the standard of care and will need to be addressed before implementing a change in care. The benefits of intramuscular midazolam include: stability at room temperature and the relative ease and reliability of delivery.

VENTRICULAR PERITONEAL SHUNT: RAPID MRI FOR SHUNT OBSTRUCTION

In pediatric patients ≤ 21 years of age presenting to the emergency department with a suspicion for a Ventricular Peritoneal (VP) shunt malfunction, is a rapid cranial MRI non-inferior to cranial CT for identifying VP malfunction?

Joshua Beiner, M.D., Adriana Manikian, M.D.
July 2014

Boyle TP, Paldino MJ, Kimia AA, Fitz BM, Madsen JR, Monuteaux MC, Nigrovic LE.

COMPARISON OF RAPID CRANIAL MRI TO CT FOR VENTRICULAR SHUNT MALFUNCTION.

Pediatrics. 2014 Jul;134(1): e47-54.
PubMed ID: 24918222

STUDY DEFINITIONS	
POPULATION	Inclusion: Consecutive ED visits, patients ≤ 21years, any type of ventricular shunt, recommended for imaging by attending Neurosurgeon for possible shunt malfunction Exclusion: Neuroimaging for reasons other than VS malfunction (e.g., infection), neuroimaging at outside facility or prior to ED encounter, repeat visits within 6 days of study inclusion, repeat visits within 2 days of surgical VS revision. Setting: Single academic medical center. 5/2010-8/2013
TEST	Rapid Cranial MRI (rMRI) or Non-Contrast Head CT (NCHCT)
REFERENCE STANDARD	VS Malfunction: Need for operative revision for relief of mechanical causes of altered shunt flow within 72 hours of ED evaluation.
OUTCOME	Test characteristics of rMRI and cranial CT
DESIGN	Observational: Retrospective cohort study (non-inferiority hypothesis)

ARE THE RESULTS VALID?	
Did participating patients present a diagnostic dilemma?	Yes. Patients presented a diagnostic dilemma. The diagnosis of VP malfunction can present with symptoms that may mimic a more benign illnesses.
Did investigators compare the test to an appropriate, independent reference standard?	Yes and No. The reference standard, neurosurgical intervention, was performed on only 22% (153/698) of patient as it would clearly un unethical to perform surgery on all patients. Imaging was compared to operative findings and final diagnosis was based on need for relief of mechanical causes of altered shunt flow alone. 6/153 (3.9%) patients had a normal neurosurgical exploration and 8/153 (5.2%) patients required revision for reasons other than VS malfunction (e.g., infection, subdural hematoma, over-drainage) resulting in a 9.2% (14/153) negative VS malfunction rate.
Were those interpreting the test and reference standard blind to the other results?	Unlikely fully blinded. As the study was retrospective, the initial radiologic interpretation was made by clinical radiologists during ED evaluation. It was not specified whether they received clinical details at the time, Level of training was also not reported. Study radiologists, who were blinded to patient information and previous interpretations, reviewed only the “Ambiguous” imaging and dichotomized the results into “Normal” or “Abnormal”. 20% of the initial interpretations were ambiguous (51% CT, 49% rMRI), and 34% of these ambiguous studies were assessed as “Abnormal” after study radiologist review. These results suggest that a large proportion of imaging is ambiguous in real-time.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	Yes and No. Neurosurgical intervention was performed on a minority of patients (22%) for reasons detailed above. For those patients who did not require surgical intervention, ED imaging was compared to the last baseline neuroimaging. The rMRI group’s test characteristics were compared to those of the CT group, and the CT group was also compared to previously published test characteristics. The imaging study was compared to the most recent baseline neuroimaging, whether CT or rMRI. Therefore, the intervention of interest was also being used as the reference standard to make the diagnosis.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

		VP SHUNT MALFUNCTION		
		YES	NO	
HEAD CT	POSITIVE	46	36	82
	NEGATIVE	24	229	253
		70	265	335

Likelihood Ratio (+) Test: (46/70)/(36/265) = 4.83, 95% CI (3.42, 6.85)
Likelihood Ratio (-) Test: (24/70)/(229/265) = 0.4, 95% CI (0.29, 0.55)

		VP SHUNT MALFUNCTION		
		YES	NO	
RAPID MRI	POSITIVE	36	32	68
	NEGATIVE	34	260	294
		70	292	362

Likelihood Ratio (+) Test: (36/70)/(32/292) = 4.7, 95% CI (3.15, 7.0)
Likelihood Ratio (-) Test: (34/70)/(260/292) = 0.54, 95%CI (0.43, 0.69)

<u>Secondary Outcome: Need for Sedation</u>
Rapid MRI: 0.6%
CT: 7% group, $p < 0.001$

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	Yes. We have similar issues, Lack of a neurosurgical reference standard for all cases, lack of readily available rMRI capabilities 24/7 and longer time to coordinate MRI as compared to CT. For rapidly deteriorating patients, the more readily accessible imaging modality will need to be ordered, which is generally CT. Inter-rater reliability for image interpretation as not reported though interpretation of change in ventricle size when a prior comparison study is available should be reliable,
Are the study results applicable to the patients in my practice?	Yes. The range and prevalence of diagnoses seems in line with what is treated in our institution, and all conditions with ventricular shunts have the potential for malfunction.
Will the results change my management strategy?	Prior to this study, the trend at our institutions has been towards selecting rMRI in evaluating suspected VS malfunction. Given the comparable results and the added benefits of MRI over CT, I would not opt for CT except perhaps in an unstable patient where CT is more available.
Will patients be better off as a result of the test?	Yes. rMRI was not inferior to CT for evaluating ventricular size and spares a susceptible patient from a large radiation burden at only a slightly larger monetary and time expense.

CLINICAL BOTTOM LINE

BACKGROUND: Ventricular shunting is the treatment of choice for pediatric hydrocephalus arising from a broad number of etiologies. Given the tendency of ventricular shunts to malfunction or become infected, these patients undergo numerous evaluations over the course of a lifetime. Traditionally, imaging has relied on a non-contrast head CT scans with or without a shunt series. The test characteristics of non-contrast head CT to detect ventricular shunt malfunction are (Sensitivity 54-80%, Specificity 80-90%) as malfunction with intracranial hypertension does not produce ventriculomegaly in all cases.

CLINICAL QUESTIONS: In pediatric patients ≤ 21 years of age presenting to the emergency department with a suspicion for VP shunt malfunction, is a rapid cranial MRI non-inferior to cranial CT for detecting ventricular shunt (VS) malfunction?

DESIGN/VALIDITY: The study was retrospective cohort of patients with suspected ventriculoperitoneal shunt malfunction. The primary analysis included 286 patients with 698 ED visits. Slightly more than one-fifth (22%) of the patients received the reference standard of neurosurgical intervention. The CT group that was clinically “sicker”. Since not all patients received a non-contrast head CT, the control and reference standard was operative intervention for ventricular shunt malfunction. Ethically, only those with radiographic or clinical suspicion could be taken to the OR, so clinical follow-up was the reference standard for non-operative patients.

PRIMARY RESULTS: rMRI was non-inferior to CT. Test characteristics of rMRI were similar to both study and literature CT test characteristics (Sensitivity 51.4%, 95% CI (40, 62.8%), Specificity 89%, 95% CI (84.9, 92.1%); PPV 52.9%, 95% CI (40.5, 65%), NPV 88.4%, 95% CI (84, 91.8%), LR(+) 4.7, 95% CI (3.2, 7); LR(-) 0.54, 95% CI (0.43, 0.69). The “Time Interval” outcome of interest was “Image Order to Completion,” which reiterated the long time it takes to coordinate a rMRI study in daily practice. The significant “ED Arrival to OR” time difference was likely a reflection of the sicker patients being in the CT group.

APPLICABILITY: The range and prevalence of diagnoses seems in line with what is treated in our institution, and all conditions with ventricular shunts have the potential for malfunction. The availability of rMRI in a timely manner and acceptance of rMRI in lieu of a non-contrast head CT by our neurosurgery colleagues may limit applicability in some settings.

AUTHOR’S CONCLUSION: “The use of rapid cranial MRI to evaluate possible ventricular shunt malfunction increased dramatically over the study period. Rapid cranial MRI accuracy was not inferior to that of CT for diagnosing ventricular shunt malfunction and has the advantage of sparing ionizing radiation exposure in children with shunted hydrocephalus. However, the time to obtain neuroimaging was slightly longer for ED visits where rapid cranial MRI was performed. As in- creased familiarity extends use of rapid cranial MRI to a wider spectrum of patients with potential shunt malfunction, sensitivity of rapid cranial MRI for this diagnosis and neuroimaging time should be revisited.”

POTENTIAL IMPACT: This study, despite some methodological limitations, demonstrated that accuracy and specificity of rMRI were non-inferior to non-contrast head CT. Given the enormous advantage of sparing patients the radiation of CT, rMRI should be preferable to non-contrast head CT. However, until rMRI is as readily available as CT, CT will likely remain the imaging modality of choice for the small subset of rapidly deteriorating patients in need of emergent imaging.

OBSTETRICS & GYNECOLOGY

1. Ectopic Pregnancy: RUQ POCUS: Acad Emerg Med 2007
2. Ovarian Torsion: Rule Derivation: Arch OB-GYN 2018

ECTOPIC PREGNANCY:
RUQ POINT OF CARE ULTRASOUND

In women in their first trimester of pregnancy presenting to the ED with abdominal pain or vaginal bleeding, what are the test characteristics of trans-abdominal, pelvic and right upper quadrant point of care ultrasound performed by emergency physicians in identifying ectopic pregnancy requiring operative intervention?

Jeffrey Dela Cruz, M.D., Michael Mojica, M.D.

February 2014

Moore C, Todd WM, O'Brien E, Lin H.

FREE FLUID IN MORISON'S POUCH ON BEDSIDE ULTRASOUND PREDICTS NEED FOR OPERATIVE INTERVENTION IN SUSPECTED ECTOPIC PREGNANCY.

Acad Emerg Med. 2007 Aug;14(8):755-8.
PubMed ID: 17554008

STUDY DEFINITIONS

POPULATION	Inclusion: Female patients, positive pregnancy test, first trimester with abdominal pain and/or vaginal bleeding, intended to obtain imaging or consultation. Exclusion: None specified Setting: Single, Academic Medical Center ED, 2/2003-1/2004
TEST	Point of care ultrasound: Transabdominal: Pelvic and RUQ (Morrison's Pouch) Enrolling physicians: 3-hour training course or equivalent training Morison's pouch: Positive, negative, or indeterminate. Pelvic Ultrasound: Intrauterine pregnancy (IUP) or no definitive IUP Fluid in the cul-de-sac: Present or absent
REFERENCE STANDARD	Non-ectopic or ectopic pregnancy, operative or medical management Radiologist performed transvaginal ultrasound Review of the medical charts for radiology ultrasound findings, operative records, online medical records, and/or telephone conversations
OUTCOME	Test characteristics
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?

Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. The patients were suspected of having an ectopic pregnancy based on the stage of pregnancy (1st trimester) and symptoms. Table 2 indicates that in patients with ectopic pregnancy had a normal mean blood pressure and heart rate. Table 2 compares patients with ectopic pregnancy requiring and not requiring operative intervention. Unfortunately, it does do compare either group or the patients with ectopic pregnancy to those without ectopic pregnancy. This would allow us to determine if ectopic pregnancy was more clinically apparent.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The point of care ultrasound was compared to trans-vaginal radiology US, operative intervention, or clinical follow-up
Were those interpreting the test and reference standard blind to the other results?	Yes and No. ED physicians performing US were blinded to ultimate diagnosis of ectopic or intrauterine pregnancy. It is not specifically stated if the radiologist and obstetricians were aware of the ED ultrasound findings though that it is highly likely that there were not blinded. Follow-up was performed by 1 of 4 study investigators blinded to ED ultrasound results.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	No. 12/242 (4.9%) did not receive radiology US or operative intervention and were discharged with a diagnosis on intrauterine pregnancy on ED US. 4/242 (1.6%) were diagnosed with ectopic on ED US and taken directly to OR (no radiology ultrasound performed). Unknown if ectopic diagnosed by fluid in Morison's or from free fluid in pelvis influenced the decision to go to the OR (possible verification bias)

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 242
28/242 (11.5%) with ectopic pregnancy
18/242 (7.4%) with ectopic requiring operation
Average time of scan 4.5 minutes

		ECTOPIC PREGNANCY REQUIRING OPERATION		
		YES	NO	
ED ULTRASOUND RUQ FLUID	YES	9	1	10
	NO	9	222	231
		18	223	241

Prevalence: 18/241 = 7.4%
Sensitivity: 9/18 = 50%, 95% CI (27, 73%)
Specificity: 222/223 = 99.5%, 95% CI (97, 100%)
Predictive Value (+) Test: 9/10 = 90%, 95% CI (60, 98%)
Predictive Value (-) Test: 222/231 = 96%, 95% CI (93, 98%)
Likelihood Ratio (+) Test: (9/18)/(1/223) = 112, 95% CI (15, 831)
Likelihood Ratio (-) Test: (9/18)/(222/223) = 0.5, 95% CI (0.3, 0.8)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Unclear. The authors state that the scans were reviewed by the principle investigator but a kappa statistic was not reported for either adequate image acquisition or image interpretation. Physicians with a range of ultrasound experience were involved in the study.
Are the study results applicable to the patients in my practice?	Perhaps. We see a large number of young women in their first trimester with a complaint of abdominal pain and/or vaginal bleeding. Clinical data on the patients without an ectopic pregnancy would have been useful to determine applicability. The overall prevalence of ectopic pregnancy in this study is 11.5% while the typical rate in the ED literature is 7-8%.
Will the test results change my management strategy?	Yes. Our experience with the FAST exam would make a RUQ abdominal view an easy addition to the standard transvaginal ultrasound.
Will patients be better off as a result of the test?	Yes. Patients may experience less of a delay in definitive operative care if the RUQ ultrasound is positive for fluid. This would depend on the OB consultant. In this study 1 in every 24 patients had a positive RUQ ultrasound.

CLINICAL BOTTOM LINE

BACKGROUND: Abdominal pain and/or vaginal bleeding is a common presenting complaint in women in the first trimester of pregnancy. The primary concern is the identification of an ectopic pregnancy and more importantly the identification of ectopic pregnancy requiring urgent operative intervention.

CLINICAL QUESTION: In pregnant women in their first trimester presenting to the ED with abdominal pain or vaginal bleeding, what are the test characteristics, of point of care trans-abdominal, pelvic and right upper quadrant (RUQ) ultrasound performed by emergency physicians in identifying ectopic pregnancy requiring operative intervention?

DESIGN/RISK OF BIAS: This study was an observational prospective cohort study enrolling consecutive patients at a single urban center. There are several validity concerns with the study's methodology. The study would have benefited from a description of patients without ectopic pregnancy to compare with those with ectopic pregnancy. In addition, the consultants (radiologist and obstetrics/gynecology) were not blinded to the point of care ultrasound results. In the case of the OB/GYN consultant, knowledge of the ultrasound findings could influence the decision to go to the operating room (verification bias). Reference standards were not performed on all patients. 12/242 (4.9%) did not receive radiology ultrasound or operative intervention. 4/241 (1.6%) did not receive radiology US but received operative intervention.

Only point of care transabdominal ultrasound was performed. Transabdominal ultrasound is less accurate than transvaginal pelvic ultrasound in identifying free fluid. Ultrasound interpretation is subject to spectrum bias with a higher sensitivity in those with a greater amount of free fluid. The amount of fluid seen in the RLQ was classified only as positive, negative, or indeterminate.

PRIMARY RESULTS: The study enrolled 242 patients of which 28 (11.6%) had an ectopic pregnancy. 18 (64%) of the 28 patients with an ectopic pregnancy underwent operative intervention within 24 hours of presentation (7.4% of the total population). The average duration of the point of care ultrasound was 4.5 minutes.

The presence of fluid on the RUQ trans-abdominal ultrasound correctly identified 50% (27,73%) of the patients requiring operative intervention. The low number of patients requiring operative intervention resulted in a very wide confidence interval. The absence of fluid on the RUQ Trans-abdominal ultrasound correctly identified 99.5%, 95% CI (97, 100%) of the patients not requiring operative intervention. The authors did not present then number of patients in which free fluid was found in the RUQ and not in the pelvis. It is difficult to determine the utility of adding a RUQ view to the transabdominal pelvic ultrasound without this data.

APPLICABILITY: The results of the study appear applicable to our patients. The prevalence of ectopic pregnancy in this study was higher than typically reported in the literature. Since the right upper quadrant transabdominal ultrasound is learned as part of the FAST exam it would not be difficult to add it to the transvaginal sono that Is currently done in these patients. Patients with ectopic requiring operative management could benefit by rapid determination of free fluid in the right upper quadrant. It would have been helpful to determine the reproducibility of the ultrasound findings.

AUTHOR'S CONCLUSION: "Free intraperitoneal fluid found in Morison's pouch in patients with suspected ectopic pregnancy may be rapidly identified at the bedside by an emergency physician-performed ultrasound and predicts the need for operative intervention. Trans-abdominal pelvic ultrasound may show an intrauterine pregnancy in more than one third of patients with suspected ectopic pregnancy."

POTENTIAL IMPACT: There was a small study of patients requiring operative management of ectopic pregnancy (n=19). There are several validity concerns that limit the usefulness of the study's finding. However, there is little downside to adding an additional view to the pelvic ultrasound if the interpretation of the scan is reproducible. The presence of fluid in the RUQ may facilitate the consults decision for operative intervention.

OVARIAN TORSION:
DECISION RULE DERIVATION

In women older than 16 years of age undergoing laparotomy for suspected ovarian/adnexal torsion can demographic,clinical, laboratory and ultrasound findings predict those with and without ovarian/adnexal torsion?

Kyle Pasternac, MD, Elicia Skelton, MD,
Michael Mojica, MD
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Melcer Y, Maymon R, Pekar-Zlotin M,
Vaknin Z, Pansky M, Smorgick N.

DOES SHE HAVE ADNEXAL TORSION? PREDICTION OF ADNEXAL TORSION IN REPRODUCTIVE AGE WOMEN.

Arch Gynecol Obstet. 2018 Mar; 297(3):685-690.
PubMed ID: 29270727

STUDY DEFINITIONS	
POPULATION	Inclusion: > 16 years of age undergoing laparotomy for suspected ovarian torsion Exclusion: < 16 years, pregnant, post-menopausal, chronic pelvic pain, emergent laparotomy for other indications Setting: Single Academic Center (Israel), 1/2008-12/2014.
RULE PARAMETERS	Demographic: Age Clinical Presentation: Duration of pain prior to presentation, location of pain (RLQ, LLQ, diffuse), nausea and/or vomiting, fever, history of prior negative laparotomy for suspected torsion Physical Exam: Peritoneal signs Laboratory Tests: WBC, CRP Ultrasound (without color Doppler). See appendix for definitions of findings Free fluid, adnexal edema, benign cystic teratoma, para-ovarian cyst, hemorrhagic corpus luteal cyst, other adnexal cystic, no adnexal pathology Ultrasound performed by GYN attending and/or resident with a wide range of ultrasound experience. Ultrasound reports were reviewed. Ultrasound images were not reviewed
REFERENCE STANDARD	Surgical findings and pelvic pathology from operative report Torsion defined as: “adnexal vessels (i.e., the ovarian ligaments and the utero-ovarian ligaments) were twisted, and the adnexa appeared enlarged, edematous and sometimes bluish.”
OUTCOME	Odds ratios from logistic regression analysis Area under the ROC curve
DESIGN	Retrospective cohort (chart review)

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	No. See table 1 (demographic, clinical and lab) and table 2 (ultrasound). Demographic: Arbitrarily divided duration of pain prior to presentation into < 24hrs and > 24hrs Exam: Did not include pain score or pelvic exam findings Ultrasound: Color Doppler not assessed. Together these are many of the factors that we consider and should have been included.
Were all important predictors present in significant proportion of the study population?	No. (See Tables 2 and 3). There was a low prevalence of the following potential predictors: fever (2.5%), prior negative Lap for suspected torsion* (4%), para-ovarian cyst (6.5%), benign cystic teratoma (7%)*, normal ovary on US* (8%), peritoneal signs* (13.6%). It is difficult to assess the impact of these factors given their low prevalence. An * indicates a significant independent predictors of torsion in the regression analysis.
Were the outcome event and predictors clearly defined?	Yes. See appendix but unclear if definitions are ones that were used by this group or ones generally accepted in the ovarian torsion and ultrasound literature. Torsion defined as: “adnexal vessels (i.e., the ovarian ligaments and the utero-ovarian ligaments) were twisted, and the adnexa appeared enlarged, edematous and sometimes bluish.” In addition, the proportion of patients that met each of the operative findings defining of torsion were not presented.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Yes. Clinical, lab and ultrasound results were available before laparotomy findings. Unclear. Those performing the laparotomy were likely <u>not</u> blinded to the clinical, lab or ultrasound findings. It is unclear though unlikely if this knowledge would affect the determination of the presence or absence of torsion.
Was the sample size adequate (including an adequate number of outcome events)?	Yes. Greater the 10 cases of torsion for each predictors. 8 significant predictors in regression analysis and 111 with torsion (13.8 torsions per predictor)

WHAT ARE THE RESULTS?

N = 199
Torsion: 111/199 (55.8%). Therefore, negative laparotomy rate of 44.2%
Table 1 (demographic, clinical and labs) and Table 2 (ultrasound findings) provide the bi-variable comparisons and those with and without torsion.

Logistic Regression Analysis
8 independent predictors of torsion (5 ultrasound, 2 clinical, 1 laboratory) (See Table below)
7 independent predictors associated with an increased odds of ovarian torsion (odds ratio > 1)
1 independent predictors associated with a decreased odds of ovarian torsion (odds ratio < 1)
Two predictors that were found to be statistically significant in the bivariable analysis (duration of abdominal pain and prior history of a negative laparotomy for suspected torsion) do not appear to be included in the regression analysis.
Age and normal appearance of the ovary on ultrasound were not independent predictors of torsion.

Area under the curve = 0.93, 95% CI (0.90, 0.97%).
Rule characteristics or a scoring system to use the rule were not presented

INDEPENDENT PREDICTORS	TYPE	ADJUSTED OR (95% CI)
Complaint of Nausea/Vomiting	Clinical	4.5 (1.8, 11.1)
Peritoneal signs	Clinical	110.9 (4.2, 2,421.9)**
WBC > 11	Lab	3.7 (1.3, 10.8)
Free fluid	Sono	34.4 (6.7, 177.9)**
Ovarian edema	Sono	4.2 (1.5, 11.6)
Benign cystic teratoma	Sono	7.8 (1.2, 49.4)**
Corpus luteum cyst	Sono	0.04 (0.008, 0.2)*
Right side pathology	Sono	4.7 (1.9, 11.9)
*An adjusted odds ratio of < 1 indicates a decreased risk of ovarian torsion **Note the very wide confidence intervals due to their low prevalence		

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SENSITIVITY AND PREDICTIVE VALUE OF A NEGATIVE RULE WITH 95% CONFIDENCE INTERVALS)
Rule characteristics were not presented and are not calculable from the available data
HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SPECIFICITY AND PREDICTIVE VALUE OF A POSITIVE RULE WITH 95% CONFIDENCE INTERVALS)
Rule characteristics were not presented and are not calculable from the available data
HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?
Potential impact on resource utilization was not presented and is not calculable from the available data
WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?
Internal validation of the rule was not performed.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (See Appendix)	☐ I ☐ II ☐ III ■ IV This is a stage IV rule (derivation only) and requires further validation before it can be applied clinically.
Does the rule make clinical sense?	Yes. It does make sense that the independent predictors identified are associated with an increased or decreased risk of ovarian torsion. However, it is unclear why right sided pathology on ultrasound is associated with an increased risk.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. This was a retrospective cohort. An assessment of inter-rater reliability would have been helpful for ultrasound interpretation given varying experience levels. The authors could have reviewed the ultrasound images and not just the ultrasound report. It also would have been helpful to assess Inter-rater reliability for the reference standard of operative findings consistent with torsion.
Is the rule applicable to the patients in my practice?	No. This was a select group of patients who all went for laparotomy. We evaluate patients prior to this decision being made in consultation with our GYN consultants. In addition, many of the factors that we utilize in the clinical decision making process such a pain severity, pelvic examination findings and doppler ultrasound assessment for blood flow were not included as potential predictors. Finally, it is unclear is the study's findings are generalizable to pediatric patients younger than 16 years of age.
Will the rule results change my management strategy?	No. Not at this stage of development and not given the flaws in design and applicability that were identified.
What are the benefits of applying the rule to my patients?	There is a theoretical benefit in decreasing the negative laparotomy rate. Recommendation on how to utilize the independent predictors as a clinical decision rule were not provided and the potential impact on the negative laparotomy rate was not assessed.
What are the risks of applying the rule to my patients?	There is always a potential for missing patients with torsion. Without the rule characteristics it is impossible to assess the likelihood of this.

CLINICAL BOTTOM LINE

BACKGROUND: The differential diagnosis of lower abdominal pain in women is extensive. Missed ovarian torsion can have a long term impact on fertility. Unfortunately, there are no demographic, clinical, ultrasound findings that can reliably exclude the diagnosis of torsion. Approximately 50% of women undergoing laparotomy for suspected torsion will not have torsion. An accurate clinical decision rule identifying those at low risk for torsion could potentially reduce the negative laparotomy rate without an increased rate of missed ovarian torsion.

CLINICAL QUESTION: In women older than 16 years of age undergoing laparotomy for suspected ovarian/adnexal torsion can demographic, clinical, laboratory and ultrasound findings predict those with and without ovarian/adnexal torsion?

DESIGN/RISK OF BIAS: This was a single academic center retrospective cohort of women undergoing laparotomy for suspected ovarian torsion. The primary validity concern is that factors utilized in the clinical decision making process such a pain severity, pelvic examination findings and doppler ultrasound assessment for blood flow were not included as potential predictors. Operative findings consistent with ovarian torsion was defined as: adnexal vessels twisted, adnexa enlarged and edematous or blue discoloration. It is unclear if this is the standard definitions for adnexal torsion operative findings.

PRIMARY RESULTS: The study included 199 women undergoing laparotomy for suspected torsion of which 111 (55.8%) had operative findings consistent with torsion. The logistic regression analysis identified 8 independent predictors of torsion (5 ultrasound, 2 clinical, 1 laboratory). 7 independent predictors associated with an increased odds of ovarian torsion (odds ratio > 1) and 1 independent predictor (corpus luteal cyst identified on ultrasound was associated with a decreased odds of ovarian torsion (odds ratio < 1). Two predictors that were found to be statistically significant in the bivariable analysis (duration of abdominal pain and prior history of a negative laparotomy for suspected torsion) do not appear to be included in the regression analysis. Age and normal appearance of the ovary on ultrasound were not independent predictors of torsion. That is worth repeating. A normal ultrasound was not an independent predictor of torsion.

The area under the receiver operative characteristics curve was 0.93, 95% CI (0.90, 0.97%) indicating a high degree of diagnostic accuracy. The Rule characteristics or a scoring system to use the rule were not presented.

SIGNIFICANT PREDICTORS	TYPE	ADJUSTED OR (95% CI)
Complaint of Nausea/Vomiting	Clinical	4.5 (1.8, 11.1)
Peritoneal signs	Clinical	110.9 (4.2, 2,421.9)**
WBC > 11	Lab	3.7 (1.3, 10.8)
Free fluid	Sono	34.4 (6.7, 177.9)**
Ovarian edema	Sono	4.2 (1.5, 11.6)
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Corpus luteum cyst	Sono	0.04 (0.008, 0.2)*
Right side pathology	Sono	4.7 (1.9, 11.9)
*An adjusted odds ratio of < 1 indicates a decreased risk of ovarian torsion **Note the very wide CI due to their low prevalence		

APPLICABILITY: This was a select group of patients who all went for laparotomy at a single academic center. We evaluate patients prior to the operative decision being made in consultation with our GYN consultants. It is unclear if the study's findings are generalizable to pediatric patients younger than 16 years of age. An assessment of inter-rater reliability would have been helpful for ultrasound interpretation given varying skill levels and for the reference standard of operative findings consistent with torsion. The authors could have reviewed the ultrasound images and not just the ultrasound report. This is a stage IV rule (derivation only) and requires further validation before it can be applied clinically.

AUTHOR'S CONCLUSION: "In conclusion, various clinical, sonographic and laboratory findings on the routine evaluation of women with suspected adnexal torsion may be used to support this diagnosis and could be incorporated into the daily emergency room workup of women with acute abdominal pain."

"Our findings may be used to differentiate between women who are more or less likely to have adnexal torsion, but cannot replace laparoscopy as the definite diagnostic and treatment modality. Thus, laparoscopy should be considered in all young women with suspected torsion because of the significant sequela of missed diagnosis in this population."

POTENTIAL IMPACT: The findings of this study should not impact clinical decision making at this stage of rule development and given the risks of bias in design and applicability that were identified.

APPENDIX: ULTRASOUND FINDINGS CLASSIFICATION

Free fluid in the cul-de-sac	Considered significant when the amount of fluid was more than minimal, i.e., extending to at least half of the uterine corpus.
Adnexal edema	Enlarged hyperechogenic ovary with multiple small follicles in the ovarian periphery and stromal edema (recognized as an echogenic stroma)
Benign cystic teratoma	Diffusely or partially echogenic mass causing acoustic shadowing, possibly containing multiple echogenic strands produced by hair in the cyst cavity, fluid–fluid levels resulting from sebum and aqueous fluid in the cyst cavity, and echogenic components produced by adipose tissue and calcification in the dermoid plug
Paraovarian cyst	Thin-walled cyst with anechoic contents separate from the ipsilateral ovary
Hemorrhagic corpus luteum cyst	A cyst with homogeneous or heterogeneous echogenic content
Other cysts	Adnexal cysts which could not be classified in the previous groups.
No pathology	No adnexal findings of the previous groups

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

ORTHOPEDICS

1. Ankle Fracture:Decision Rules: Ann Emerg Med. 2009
2. Ankle Fracture: Removable Splints: Ped Emerg Care. 2012
3. Elbow Fracture: Point of Care Ultrasound: Annals EM. 2013
4. Forearm Fractures: Amsterdam Wrist Rule: Ped Rad 2018
5. Forearm Fracture: POCUS Reduction: Ann Em Med. 2015
6. Forearm Fracture: Torus Splint: Pediatrics. 2006
7. Septic Arthritis: Rule Derivation: J Bone Joint Surg A. 1999

ANKLE FRACTURES:
ANKLE FRACTURE DECISION RULES VALIDATION

In patients, less than 16 years old with acute ankle trauma, how accurate are the Ottawa Ankle Rules, The Low-Risk Exam, and the Malleolar Zone Algorithm in identifying those with and without clinically important ankle fractures?

Sheri-Ann Wynter, M.D., Martin Pusic, MD, PhD.
March 1, 2016

Gravel J, Hedrei P, Grimard G, Gouin S.

PROSPECTIVE VALIDATION AND
HEAD-TO-HEAD COMPARISON OF 3 ANKLE RULES
IN A PEDIATRIC POPULATION.

Ann Emerg Med. 2009 Oct;54(4):534-540.
PubMed ID: 19647341

STUDY DEFINITIONS	
POPULATION	Inclusion: <16 years old presenting to an ED with non-penetrating ankle trauma sustained within the previous three days Exclusion: 1. Factors impairing physical exam: History of isolated skin injury, developmental delay, neurological impairment, intoxication, altered level of consciousness, multisystem trauma with distracting injury, history of analgesia besides acetaminophen or ibuprofen within 6 hours of presentation) and 2. Factors predisposing to fracture: Prior surgery to affected ankle, orthopedic disease, or metabolic bone disease. Setting: Single Pediatric ED, 8/2005-10/2007
RULES	Clinical Decision Rules: Ottawa Ankle Rules (OAR), Low-Risk Exam Ankle Rule (LRER) Malleolar Zone Algorithm (MZA).
REFERENCE STANDARD	Clinically Important Ankle Fracture. Defined as any fracture excluding a Salter-Harris 1 fracture of the distal fibula. Orthopedic Surgery Follow-up OR Radiographs OR Telephone Follow-up
OUTCOME	Rule's Characteristics
DESIGN	Observational: Prospective cohort

ARE THE RESULTS VALID?	
Were the patients chosen in an unbiased fashion and do they represent a wide spectrum of severity of disease?	Yes. Patients were prospectively enrolled if they presented to the ED for a non-penetrating ankle trauma within the last 72 hours. Table 1 shows that 72% had ankle sprains, 11% had a Salter I fracture of the fibula (not included in definition of clinically important fractures) and 17% had a clinically important ankle fracture.
Was there a blinded assessment of the criterion standard for all patients?	Yes. There was blinded assessment in this study. The authors note that each clinician recorded specific elements of the history and physical on a standardized data form, and the indication to proceed to radiography according to each of the three rules was completed before radiology.
Was there an explicit and accurate interpretation of the predictor variables and the actual rule without knowledge of the outcome?	Yes. ED members received a 1-hour presentation of how to apply ankle rules prior to the initiation of patient recruitment. Each physician was also personally instructed by one of the study investigators on patient assessment using the three rules. Each data form also had a schematic of the three ankle rules.
Was there 100% follow up of those enrolled?	No. Most patients were referred to an Orthopedic Surgeon for follow-up in clinic, but some were not, and had telephone follow-up instead. However, there were 5 out of the 272 enrolled patients who did not have clinic follow-up, and could not be reached for telephone follow-up (98% follow up)

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SENSITIVITY AND PREDICTIVE VALUE OF A NEGATIVE RULE WITH 95% CONFIDENCE INTERVALS)

OTTAWA ANKLE RULE (OAR)

	FRACTURE	NO FRACTURE	
OAR POSITIVE	47	165	212
OAR NEGATIVE	0	60	60
	47	225	272

Sensitivity: 47/47 = 100%, 95% CI (93, 100%).
Predictive Value (-) Rule: 60/60 = 100%, 95% CI (99.4, 100%)

LOW RISK EXAM ANKLE RULE (LRER)

	FRACTURE	NO FRACTURE	
LRER POSITIVE	41	104	145
LRER NEGATIVE	6	121	127
	47	225	272

Sensitivity: 41/47 = 87%, 95% CI (75. 94%)
Predictive Value (-) Rule: 121/127 = 95%, 95% CI (93,98%)

MALLEOLAR ZONE ALGORITHM (MZA)

	FRACTURE	NO FRACTURE	
MZA POSITIVE	44	171	215
MZA NEGATIVE	3	54	57
	47	225	272

Sensitivity: 44/47 = 94%, 95% CI (83, 98%).
Predictive Value (-) Rule: 54/57 = 95%, 95% CI (92, 97%)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SPECIFICITY AND PREDICTIVE VALUE OF A POSITIVE RULE WITH 95% CONFIDENCE INTERVALS)

	SPECIFICITY	PREDICTIVE VALUE (+) RULE
OAR	27% (21-33%)	22% (15-29%)
LRER	54% (47-60%)	28% (23-34%)
MZA	24% (19-30%)	20% (16-25)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

Use of two of the three rules would decrease resource utilization with less ankle radiography being performed to evaluate for ankle fracture (Table 2. Compared to 90% baseline XRAY utilization in the study population)

REDUCTION IN XRAY UTILIZATION

RULE	XRAY REDUCTION	MISSED FRACTURE
OAR	7%	0/47 (0%)
LRER	46%	6/47 (12.8%)
MZA	4%	3/47 (6.4%)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

At what level of development is this rule? How can it be applied? (See Appendix)	The OAR is at level II stage of development with multiple validation studies done to date, but no impact analysis in children. (See Table E1). Similarly, the MZA has been validated in this study, but there has not yet been any impact analysis. The LRER is now at level I of development with impact analysis completed showing decreased radiography and health care associated cost.
Does the rule make clinical sense?	Yes. Many of the questions that make up the rule are related to objective physical exam findings, such as ability to bear weight for four steps, or tenderness at specific areas of the ankle.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	The inter-rater reliability was 0.38 for the Low-Risk Exam, 0.82 for the Malleolar Zone Algorithm, and 0.77 for the Ottawa Ankle Rules. The kappa is acceptable for the latter two, but not for the LRER. However, only 6% (17/272) of cases were assessed for inter-rater reliability, limiting conclusions that can be drawn from these numbers.
Is the rule applicable to the patients in my practice?	Yes. We see skeletally immature patients with acute ankle injuries where it is unclear if there is a fracture.
What are the benefits of applying the rule to my patients?	With the application of the OAR, we can minimize exposure to radiography for those who are low risk for clinically important fractures with very good confidence that clinically important fractures will not be missed (though the lower limit of the 95% confidence interval is 93%)
What are the risks of applying the rule to my patients?	May miss clinically important fractures if the LRER or MZA are applied.

CLINICAL BOTTOM LINE

BACKGROUND: Children with acute, non-penetrating ankle trauma present a diagnostic challenge. Their skeletal immaturity makes clinically important fractures uncommon, but there is potential long-term morbidity if significant fractures are missed. We frequently obtain radiographic imaging in the Emergency Department to evaluate for fracture even in patients who are unlikely to have a significant fracture. This results in financial costs, unnecessary radiation exposure, and increased length of ED stay. These costs might be minimized with the application of a clinical decision rule that can identify when a clinically important fracture is likely, and therefore, when it is appropriate to obtain radiography.

CLINICAL QUESTION: In patients, less than 16 years old with acute ankle trauma how accurate are the Ottawa Ankle Rules, The Low-Risk Exam, and the Malleolar Zone Algorithm in identifying those with and without clinically important ankle fractures?

DESIGN/VALIDITY: This is a prospective validation of three different ankle fracture clinical decision rules including 272 patients, 47 (17.3%) of which had a non-Salter-Harris 1 fracture. All three rules were applied to each study subject to compare how well the rule identifies the presence of a clinically important fracture. The study defined clinically important fractures as fractures that are not Salter-Harris I fractures of the distal fibula. An Orthopedic Surgeon determined the definitive presence of a fracture during an outpatient follow-up clinic visit. However, some children had telephone follow-up only, while 6% had neither Orthopedic clinic follow-up nor telephone follow-up. The presence of a fracture in those patients was based on initial radiographs only.

PRIMARY RESULTS: The Ottawa Ankle Rule (OAR) was the most sensitive at identifying clinically important ankle fractures with a sensitivity of 100%, 95% CI (93, 100%). The OAR also had the best negative predictive value: 100% of patients that had a negative OAR did not have a clinically important fracture. The OAR had the potential to decrease XRAY utilization by 7%. The Low Risk Exam Rule (LRER) (Sensitivity: 87%,95% CI (75, 94%)). and the Malleolar Zone Algorithm (MZA) (Sensitivity: 94%, 95% CI (83, 98%)) had lower sensitivities than the OAR. The MZA would not have reduced XRAY utilization in this study population. The LRER has the potential to decreased XRAY utilization by 46% but at the expense of missing 13% of the clinically important ankle fractures.

APPLICABILITY: This study is largely generalizable to other ED populations that see skeletally immature patients. Only the LRER clinical decision rule is at level I stage of development. However, in this study the kappa when applying this rule was only 0.38. Although this may be related to the lack of study clinicians' comfort and familiarity with the rule, the clinicians did undergo training prior to initiation of the study. For these reasons, this raises the question of how well the LRER rule can be applied to other populations. The fact that the LRER does miss some clinically important fractures may also limit one's willingness to use it in other populations. The inter-rater reliability was 0.82 for the Malleolar Zone Algorithm, and 0.77 for the Ottawa Ankle Rules.

AUTHOR'S CONCLUSION: "We conclude that when the Ottawa Ankle Rules, Low-Risk Exam, and Malleolar Zone Algorithm were compared in this tertiary pediatric emergency medical setting, the Ottawa Ankle Rules had superior sensitivity and the Low-Risk Exam had superior specificity for clinically important fractures. Both the sensitivity and specificity of the Malleolar Zone Algorithm were inferior to those of the Ottawa Ankle Rules. The Ottawa Ankle Rules detected all clinically important fractures in this sample, with potential radiograph reduction of 7%, whereas the Low-Risk Exam missed 6 (13%) clinically important fractures, with potential radiograph reduction of 45%."

POTENTIAL IMPACT: The Ottawa ankle rule had the highest sensitivity and the potential to decrease XRAY utilization by approximately 7% though an impact analysis has not been performed in the pediatric population.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

ANKLE FRACTURES: REMOVABLE SPLINTS

In children aged 5-15 years with low-risk ankle fractures is use of the Air-Stirrup ankle brace non-inferior to the below-knee fiberglass posterior splint in helping patients return to normal function?

Janienne Kondrich, M.D., Seema Awatramani, M.D.
September 4, 2012

Barnett PL, Lee MH, Oh L, Cull G, Babl F.

FUNCTIONAL OUTCOME AFTER AIR-STIRRUP ANKLE BRACE OR FIBERGLASS BACKSLAB FOR PEDIATRIC LOW-RISK ANKLE FRACTURES: A RANDOMIZED OBSERVER-BLINDED CONTROLLED TRIAL.

Pediatr Emerg Care. 2012 Aug;28(8):745-9.
PubMed ID: 22858744

STUDY DEFINITIONS	
POPULATION	Inclusion: 5- 15 years, clinical diagnosis of a low-risk ankle fracture defined as: 1. Avulsion fracture of the distal fibula, 2. Non-displaced Salter-Harris I (isolated tenderness over fibula growth plate and normal x-ray) or Salter-Harris type II fracture of the fibula 3. Avulsion fracture of the lateral talus. Sprain: No tenderness over the growth plate but tenderness over the distal edge of the fibula or over deltoid ligament. Exclusion: 1. Injury occurred > 72 hours prior to presentation 2. Preexisting musculoskeletal disease or surgery to the affected ankle 3. Previous ankle injury to the same ankle in the past 3 months 4. Bleeding disorder (e.g., hemophilia) or on anticoagulant therapy 5. Multisystem or multi-limb trauma 6. Fracture of distal tibia or foot 7. Fracture requiring manipulation or surgical intervention Setting: Single Children's Hospital ED (Australia), 8/2007-3/2009
INTERVENTION	Ankle brace (Air-Stirrup ankle brace (AirCast)): Available in various sizes, right and left sides, adjustable fit. Prohibits inversion and eversion. Allows dorsiflexion and plantar flexion. Easy to remove for bathing.
CONTROL	Fiberglass posterior splint (Dynacast Prelude): Cut to length, molded into place, held in place by a crepe bandage. Prevents all ankle movements. Can be removed for bathing.
OUTCOME	Primary Outcome: Change in mean functional activity as measured by the Activities Scale for Kids (modified) (ASKp) at 2 and 4 weeks (See appendix) Subgroup analysis: Age categories Secondary Outcomes: Change in: 1. Physiotherapy assessment at 2 and 4 weeks 2. Degree of pain during the first 2 weeks 3. Amount of analgesia used in the first 2 weeks 4. Ease of caring for the device used.
DESIGN	Interventional: Randomized clinical trial (Non-inferiority hypothesis)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized to either the ankle brace (also known as the Air-Stirrup or Aircast) or fiberglass posterior splint (referred to as the backslab in the study). Randomization was stratified by age group (5 – 10 and 11 – 15 years) and random block sizes of 2, 4 and 6 were used.
Was randomization concealed?	Yes. Investigators did not know the block sizes being used, presumably to conceal randomization.
Were patients in the study groups similar with respect to known prognostic factors?	The study groups were very similar on many demographic variables: Age, fracture type and baseline pain. Baseline ASKp (Activities Scale for Kids, performance version) scores were also similar between the groups. The posterior splint group had more functional impairment with a higher percentage of patients (96% vs. 77%) non-weight bearing when evaluated for the injury in the ED.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Both the reviewing consultants (ED physicians not involved in the patients' initial care) who evaluated the study patients on follow-up visits at 2 and 4 weeks and the study physiotherapist were blinded. Patients removed their immobilization devices immediately prior to their follow-up appointments. The physician who initially saw the patient in the ED, the research assistants, patients and parents were not blinded.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	For the most part. Study participants had two follow-up appointments, at two and four weeks after initial injury. Nine percent 2/22 (9%) of the patients in ankle brace group and thirteen percent 3/23 (1.3%) in the posterior splint group were lost to follow-up.
Were patients analyzed in the groups to which they were randomized?	Yes. All patients seemed to have received their assigned treatment, and analysis was by the intention to treat principle.
Was the trial stopped early?	Yes. The investigators had difficulty recruiting enough patients in a timely fashion, as they had anticipated a higher number of low-risk ankle fractures during the study period. 64 patients per study group were required by the sample size determination. A total of 45 patients were randomized and 40 were included in the analysis.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 55 patients, 5 lost to follow-up
60% Salter Harris 1 fracture of the distal fibula

Primary Outcome: ASKp scores (Activities Scale for Kids) at 2 and 4 week follow-up (median +/- interquartile range)
At 2 and 4 weeks, the ankle brace group had slightly higher median ASKp scores that were both

	ANKLE BRACE N=20	BACK SLAB N=20
Baseline*	97.1 (93.9, 98.7)	94.5 (91.7. 99.3)
2 weeks	60.6 (46.8, 72.8)	56.0 (44.3. 62.3)
4 weeks	91.9 (75.7, 98.0)	84.2 (70.6. 92.6)
Baseline-4 weeks	5.2	10.3
*Baseline = Activity score during the week prior to injury		

clinically and statistically similar to the posterior splint group

Secondary Outcomes
No statistically significant difference for brace vs. splint groups, or by fracture type was found.
There was no difference in the patient with Salter-Harris 1 fractures.
Analgesic use was similar.

The only statistically significant comparison was the ankle brace group of 11 – 15 year olds who had higher ASKp scores at 2 weeks.

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence intervals for the primary outcome were reported graphically, not numerically in Figure 2.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. We frequently see children with low-risk ankle fractures, many of which are Salter Harris I fractures vs. ankle sprain. Our institution uses very similar although not identical immobilization devices (Aircast and plaster splints) to those used in the study (Air-Stirrup and fiberglass splint material).
Were all patient important outcomes considered?	Yes. The ASKp is likely a more complex measurement of functionality than simply weight bearing alone.
Are the likely treatment benefits worth the potential harm and costs?	Maybe. A slightly higher percentage of patients in the ankle brace group (50% vs. 25%) experienced pressure-related blisters and marks, although many of the ankle-brace patients did not use the protective sock they were given to prevent such complications. A comparison of the cost of each immobilization device was not given.

CLINICAL BOTTOM LINE

BACKGROUND: Ankle fractures occur commonly in school-age children and adolescents. Although variation exists between clinicians and emergency departments in the treatment of these fractures, there is evidence that less immobilization of the ankle joint results in an earlier return to baseline function.

CLINICAL QUESTION: In children aged 5-15 years with low-risk ankle fractures is use of the Air-Stirrup ankle brace non-inferior to the below-knee fiberglass posterior splint in helping patients return to normal function?

DESIGN/VALIDITY: This single-center, non-inferiority, randomized controlled trial aimed to compare two treatments of low-risk ankle fractures that encourage early mobilization: The Air-Stirrup ankle brace versus the fiberglass posterior splint. The Air-Stirrup prohibits inversion and eversion but allows dorsiflexion and plantar flexion; the posterior splint prevents all movements of the ankle. The primary validity concern is the small number of patients included

PRIMARY RESULTS: Both devices were statistically similar in terms of the primary outcome: functional activity, as measured by ASKp scores at 2 weeks and 4-weeks post-injury. The authors report that this difference was clinically similar as well but this assertion is not supported by the data presented. The authors defined in the sample size determination that the Air-Stirrup would be non-inferior if it was no more than 5% less effective than the posterior splint based on the ASKp scores at 4 weeks. The mean change in ASKp was a decreased of 5.2 in the Air-Stirrup group and 10.3 in the splint group. The difference is 5.1 in favor of the Air-stirrup group though the confidence interval for the difference is not presented making it difficult to determine non-inferiority. In addition, the investigators initially sought to power the study using methods appropriate for a non-inferiority trial. However, the total subjects included the analysis (40), was significantly fewer than their initial goal of 64 subjects per treatment arm. Although this study was perhaps well-designed it was not adequately powered to demonstrate that the ankle brace was non-inferior, and may have missed small but important treatment benefits of the standard treatment, the fiberglass posterior splint.

APPLICABILITY: The data presented represents experience at a single children's hospital ED included a total of 40 patients in the primary analysis possibly limiting the generalizability of the study's results.

AUTHOR'S CONCLUSION: "Pediatric patients with low-risk ankle fractures treated with either the Air-Stirrup ankle brace or the fiberglass posterior splint showed similar functional activity at 2 and 4 weeks regardless of treatment. The ankle brace was easier to look after and had more improvement in older children (11-15 years) at 2 but not at 4 weeks. Thus, the Air-Stirrup ankle brace is equal to the fiberglass posterior splint in returning children back to their normal levels of activities."

POTENTIAL IMPACT: This study suggested that an ankle brace such as the Air-Stirrup or the Aircast could be used interchangeably with the posterior splint in the treatment of low-risk ankle fractures. However, given concerns regarding the study's power to detect a difference between the treatments, further research is required to determine the ideal degree of mobilization of ankle injuries to allow for the quickest return to baseline function.

APPENDIX: PRIMARY OUTCOME (ASKp)

ACTIVITIES SCALE FOR KIDS (MODIFIED) WEB LINK
Self-report measure of physical disability.
5-15 years experiencing limitations in physical activity due to musculoskeletal disorders.
Contains 30 items that are aggregated into an overall summary score.
The ASKp measures what the child "did do" during the previous week.

Young NL, Williams JI, Yoshida KK, Wright JG.
Measurement Properties of the Activities Scale for Kids
J Clin Epidemiol. 2000 Feb;53(2):125-37., PubMed ID: 10729684

ELBOW FRACTURES:
POINT OF CARE ULTRASOUND

For patients 0-21 years with suspected elbow fractures how accurate is point of care ultrasound performed by the pediatric emergency physicians with limited training when compared to standard radiography and clinical follow-up in identifying those with and without elbow fractures?

Joanne Agnant, M.D., Dennis Heon, M.D.

February 2013

Rabiner JE, Khine H, Avner JR, Friedman LM, Tsung JW.

ACCURACY OF POINT-OF-CARE ULTRASONOGRAPHY FOR DIAGNOSIS OF ELBOW FRACTURES IN CHILDREN.

Ann Emerg Med. 2013 Jan;61(1):9-17.
PubMed ID: 23142008

STUDY DEFINITIONS	
POPULATION	Inclusion: < 21 years, suspected elbow fracture requiring radiographic evaluation, as determined by the attending pediatric emergency physician. Exclusion: Arrived at the ED with a radiograph already performed, previously confirmed diagnosis of elbow fracture, an open wound at the elbow, unstable vital signs or associated life-threatening injuries requiring resuscitation. Setting: 2 Pediatric EDs. 9/2010-12/2011.
INTERVENTION	Point-of-care elbow ultrasound conducted by pediatric EM faculty and fellows with 1 hours of training (1/2 didactic, ½ hour hands on) Positive elbow ultrasound: Elevation of the posterior fat pad or presence of lipohemarthrosis of the posterior fat pad.
CONTROL	Elbow XRAY with a fracture defined as “cortical irregularity” or “fracture” on the attending radiologist’s report
OUTCOME	Test characteristics
DESIGN	Observational: Prospective cohort study

ARE THE RESULTS VALID?	
Did participating patients present a diagnostic dilemma?	Not always. The authors included patients with deformity, so only some patients presented as a diagnostic dilemma. The authors reported that the pretest clinical assessment correlated with the presence of fracture, so one can argue that there was no dilemma on the part of the physicians for patients with deformity
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The criterion standard was fracture diagnosed by radiographic imaging on initial presentation and/or follow up visit. Patients who did not receive radiographic imaging on follow up received clinical follow up. This included review of the electronic medical record or structured clinical telephone follow up within a week. There were 4 patients lost to follow up, who were analyzed in the no fracture group based on negative initial POC ultrasound and XRAY.
Were those interpreting the test and reference standard blind to the other results?	Yes. The PEM physicians who enrolled and performed the POC ultrasounds did so before the radiographs were performed. The attending radiologists were blinded to the ultrasonographic findings.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	No, all patients with a negative XRAY initially and improved pain did not get a follow up XRAY. It would be unethical to expose patients to an unnecessary test.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

	ELBOW FRACTURE		
	YES	NO	
ULTRASOUND (+)*	42	26	68
ULTRASOUND (-)	1	61	62
	43	87	130
*Ultrasound (+) = Elevated posterior fat pad OR lipohemarthrosis			

Fracture prevalence = 43/130 = 33% (5/43 fractures not identified on initial visit)
Sensitivity = 42/43 = 97.7%, 95% CI (87.8, 99.6%)
Specificity = 61/87 = 70.1%, 95% CI (59.8, 78.7%)
Predictive Value (+) Test = 42/68 = 61.8%, 95% CI (49.9, 72.4%)
Predictive Value (-) Test = 61/62 = 98.4%, 95% CI (91.4, 99.7%)
Likelihood Ratio (+) Test = (42/43)/ (26/87) = 3.3, 95% CI (2.4, 4.5)
Likelihood Ratio (-) Test = (1/43)/ (61/87) = 0.03, 95% CI (0.01, 0.23)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	Yes. The Kappa statistics for the various ultrasound findings were 0.72 or higher (Table 2). This represents a strong level of agreement beyond chance. In the 4th quartile of enrollment the kappa increased to 0.94 suggesting a learning curve for the physicians.
Are the study results applicable to the patients in my practice?	Yes. Aside from gender and the physical exam, we do not have much more information regarding the demographics of the study patients. However, we have a similar ED setting in NYC so the results are likely applicable to our population.
Will the results change my management strategy?	Maybe. The use of point of care ultrasound, may reduce the use of XRAY for patients with a mechanism and examination suggest a low clinical suspicion (i.e. a low pretest probability) of elbow fracture and potentially reduce ED length of stay
Will patients be better off as a result of the test?	Unclear. We can potentially reduce radiation exposure in the 62/130 (48%) patients with a negative ultrasound. However, we may miss fractures in this group 1/43 (2%). This will have to be a judgment call by the individual clinician.

CLINICAL BOTTOM LINE

BACKGROUND: Elbow injuries are a very common presentation in the pediatric emergency department. Point of care ultrasound has proven to accurately identify long bone fractures. However, it is not well suited to identify fractures in bones with irregular contours or to distinguish between fractures and growth plates. These conditions are present in the pediatric elbow.

CLINICAL QUESTION: For patients 0-21 years with suspected elbow fractures how accurate is point of care ultrasound performed by the pediatric emergency physicians with limited training when compared to standard radiography and clinical follow-up in identifying those with and without elbow fractures?

DESIGN/VALIDITY: This was a single center prospective cohort study which included 130 patients in the primary analysis of which 47 (36.1%) had an elbow fracture on XRAY. Point of care ultrasound was considered positive if one of two indirect signs of elbow fractures were identified – elevation of the posterior fat pad or the presence of lipohemarthrosis. Pediatric emergency medicine physicians underwent one-hour total of both didactic and clinical training.

PRIMARY RESULTS: POCUS identified the majority of fractures (Sensitivity: 97.7 %, 95% CI (87.8, 99.6%). 11.5% of the patients (25% of those with fractures) had a clinically obvious deformity potentially raising the possibility of spectrum bias though the sensitivity did not decrease when patients with a deformity were not included in the analysis. Patient's with a negative point of care ultrasound were 33 times less likely to have a fracture. (LR (-) = 0.03). This may support performing a POCUS on a patient with a low pretest probability, potentially reducing the need for XRAY if the patient has reliable follow-up

47.7% (62/130) of patients in the study had a negative point of care ultrasound. These patients could potentially avoid an XRAY. However, 1.6% (1/62) of patients with a negative point of care ultrasound had a fracture that was not identified.

APPLICABILITY: The inter-rater reliability for various ultrasonographic findings was good with a kappa statistic of 0.72 or higher. In the 4th quartile of enrollment the kappa increased to 0.94 suggesting a learning curve for the physicians. Aside from gender and the physical exam, we do not have much more information regarding the demographics of the study patients.

AUTHOR'S CONCLUSION: "In summary, with focused musculoskeletal ultrasonographic training, novice pediatric emergency medicine sonologists were able to attain the skills necessary to perform point-of-care elbow ultrasonography to evaluate for fracture by assessing the posterior fat pad for elevation and lipohemarthrosis. Point-of-care ultrasonography for elevation of the posterior fat pad and lipohemarthrosis in children was found to be highly sensitive in the setting of trauma, and a negative ultrasonographic result may reduce the need for radiographs in children with elbow injuries. Pediatric emergency physician interpretations of ultrasonographic images had substantial agreement with the interpretation of an experienced pediatric emergency medicine sonologist."

POTENTIAL IMPACT: The use of point of care ultrasound may reduce the use of XRAY for patients with a mechanism and examination suggest a low clinical suspicion (i.e. a low pretest probability) of elbow fracture. We can potentially reduce radiation exposure in the 62/130 (48%) patients with a negative ultrasound. However, we may miss fractures in this group 1/62 (1.6 %). This will have to be a judgment call by the individual clinician.

It is important to note that XRAY are not obtained only to identify the presence of a fracture but also to identify fracture characteristics that would guide further management (e.g., need for reduction, length of immobilization, operative repair). A positive sonogram should likely be followed by XRAYS to be characterize the fractures.

FOREARM FRACTURES:
AMSTERDAM WRIST RULE IMPACT

In children 3-18 years of age presenting to the Emergency Department with an acute wrist injury does use of the Amsterdam Wrist Rule decrease XRAY utilization to the extent previously predicted by the prior derivation and external validation of the rule?

John Park, MD, Rebecca Burton, MD
June 2019

Mulders MAM, Walenkamp MMJ, Slaar A, Ouwehand F, Sosef NL, van Velde R, Goslings JC, Schep NWL.

IMPLEMENTATION OF THE
AMSTERDAM PEDIATRIC WRIST RULES

Pediatr Radiol. 2018 Oct;48(11):1612-1620.
PubMed ID: 29992444

STUDY DEFINITIONS	
POPULATION	Inclusion: 1. 3-18 years of age 2. Presenting to the ED 3. Acute (< 72 hours) 4. Wrist trauma: Any high or low energy accident involving the proximal hand, wrist, distal radius or distal ulna Exclusion: 1. Multiple injuries with an Injury Severity Score > 15 2. Radiographs requested prior to presentation to the emergency department 3. Previous fracture within the last 3 months Setting: Before cohort: 4/2011-4/2014, n=4 Netherlands. 1 academic hospital served as the derivation cohort. 3 teaching hospitals served as external validation cohort) After cohort (Implementation or Impact): 11/2015-6/2016, n=4 (1 academic, 3 teaching) Netherlands
RULE PARAMETERS	Rule applied using a mobile application (See Figures 1, 2 3) Application available on the Apple App Store and study website Calculator also available on the study web site: www.amsterdamwristrules.nl 1. Age 2. Gender 3. Swelling of the distal radius 4. Visible deformation 5. Distal radius is tender to palpation 6. Anatomic snuff box is tender to palpation 7. Supination is painful Based on the above parameters the application calculates the probability of a distal forearm fracture and recommends to obtain a wrist radiograph or not. The cutoff for the XRAY recommendation was a 23% risk of fracture
REFERENCE STANDARD	1. XRAY reduction: Historical cohort: 4/11-4/14 (Derivation and Validation) 2. Fracture: XRAY or phone follow-up (See Appendix)
OUTCOME	Primary Outcome: The difference in number of XRAYs before and after implementation Secondary Outcomes: 1. Missed clinically relevant fractures of the distal forearm (See Appendix) Phone follow-up 7-10 days (See Appendix) 2. Length of ED stay: Non-fracture patients: With XRAY – Without XRAY 3. Physician compliance with the rule: Yes/No. If no then why? a. Do not agree, b. Parent insist, c. Associated injury, d. Other 4. Patient/Parent satisfaction: Secure without an XRAY, willingness to wait longer in the ED to obtain an XRAY
DESIGN	Observational: After cohort (prospective), historical cohort (retrospective)

HOW SERIOUS WAS THE RISK OF BIAS?	
Was the implementation of the rule randomized?	No. The implementation was not randomized. The rule was applied consecutively to patients meeting inclusion/ exclusion criteria in both the before and after cohorts. The before cohort was from the initial derivation and external validation study.
If there was a before after design how long were the pre and post implementation phase?	The before phase was 36 months (4/2011-4/2014). The after phase was 8 months (11/2015-6/2016). There was 19 months between the end of the before phase and the beginning of the after phase. It is unclear if other changes in the approach to wrist fractures occurred in the interval between the two studies.
What was the setting in which the rule was implemented? Does the setting(s) represent a wide spectrum of severity of disease?	The After cohort was from 4 hospitals in the Netherlands (1 academic, 3 teaching). In the Before cohort, the academic hospital cohort served as the derivation population and the 3 teaching hospitals served as the external validation population. This likely represents a wide spectrum of disease severity.
What was the strategy for implementing the rule?	The rule was implemented using a phone application. The calculator and recommendations were also available through the study website.
What training was required to utilize the implementation strategy?	No training strategy was presented. However, the rule asks a series of simple questions about patient demographics and examination findings.

WHAT ARE THE RESULTS?

DEMOGRAPHIC CHARACTERISTICS

Impact (After) cohort
N=408 (84% at teaching hospitals)
Male: 52%, Median Age: 12 years, IQR (9, 14 years)
Fracture: 44.9% (radius only: 87.7%, ulna only: 0.8%, both bones: 11.5%)
Table 2: Comparison Before (Derivation + Validation) and After (Impact): No difference in age or fracture type. The before group had a statistically higher proportion of males (59.6% vs 51.7%).

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? HOW DOES THIS COMPARE TO THE RULE CHARACTERISTICS DESCRIBED IN THE DERIVATION AND VALIDATION OF THE RULE?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? HOW DOES THIS COMPARE TO THE RULE CHARACTERISTICS DESCRIBED IN THE DERIVATION AND VALIDATION OF THE RULE?

RULE PERFORMANCE[1]

	IMPACT (AFTER) (n=408)	VALIDATION (BEFORE)[3] (n=379)
Fracture Prevalence	43.1% (38.4, 48%)	44.9% (39.9, 49.9%)
Sensitivity	97.7% (94.3, 99.1%)	95.9% (91.7, 98%)
Specificity	33.2% (27.4, 39.5%)	37.3% (31, 44.1%)
Predictive Value (+) Test	52.6% (47.2, 57.9%)	55.4% (49.1, 61%)
Predictive Value (-) Test	95.1% (88, 98.1%)	91.8% (84, 96%)
Likelihood Ratio (+) Test	1.46 (1.33, 1.60)	1.53 (1.37, 1.70)
Likelihood Ratio (-) Test	0.07 (0.03, 0.18)	0.11 (0.05, 0.23)
XRAY Recommended	80% (76, 83.7%)	77.6% (73.1, 81.5%)

1. Identification of clinically relevant fractures
2. Test characteristics for the rule derivation were not presented or calculable from the data

HOW DID IMPLEMENTATION OF THE RULE IMPACT RESOURCE UTILIZATION? HOW DOES THAT COMPARE TO THE POTENTIAL IMPACT DESCRIBED IN THE DERIVATION AND VALIDATION OF THE RULE?
Potential Reduction in XRAY Utilization: Before (Derivation + Validation): 98.6% (788/799) After (Impact): 77.9% (326/408) Risk Difference (Before – After): 98.6% – 77.9% = 18.7%, 95% CI (15, 22.9%) Actual Reduction in XRAY Utilization: 6% The authors considered a 9% reduction in XRAY utilization to be clinically relevant. A potential decrease in radiographs by 22.4% was predicted in the external validation cohort.
OTHER OUTCOMES
Missed Fractures (Impact): Table 4 All: 4.5% (8/176) Clinically Relevant: 2.3% (4/176) ED Length of Stay All patients: Before: 101 minutes, IQR (73, 138min), After: 101 minutes, IQR (96, 141min) Non-fracture Patients: Had an XRAY: 68 min, IQR (39, 97 min), No XRAY: 94 min, IQR (64, 136), Risk difference: 26 minutes Physician Compliance Rule recommends no XRAY: n=81, 69% did not follow or 31% did follow rule recommendations 81 x 0.69 = 56 additional XRAYS obtained in patients the rule recommended not to 327 Recommend XRAY + 56 Obtained when not recommended = 383 XRAY obtained 383/408 = 93.4% XRAYS obtained or 6.4% actual reduction in XRAYS Reason for rule non-compliance: Suspicion of associated injury (40%), parent request (20%), physician disagreed (14%), other (25%). Physicians obtained XRAYS despite a recommendation not to in 3 of the 4 patients with clinically relevant missed fractures Patient/Parent Satisfaction All satisfied with not receiving an XRAY (except the 1 patient recalled for persistent symptoms) All would not have been happy waiting longer for an XRAY

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

At what level of development is this rule? How can it be applied? (see Appendix)	☐ I ■ II ☐ III ☐ IV This is a difficulty rule to classify. It is described as an impact analysis (Level I) but did not demonstrate a clinically significant change in physician behavior (reduction in XRAY utilization). This is likely a level II rule. Level II rules are validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. Level II rules can be used in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve. Rule characteristics in this study were similar to those in the initial validation cohort. However, this second validation occurred in the same hospitals in which the rule was derived and initially validated.
Is the strategy to implement the rule used in the study applicable to your practice setting? What are the perceived barriers to implementation?	The authors introduced a phone application to utilize the rule. Training in the use of the rule was not described. However, rule parameters were easy to assess. Both surgery residents and emergency physicians enrolled patients. It is unclear how this would translate to pediatric emergency medicine faculty or fellows.
What are the benefits of applying the rule to my patients?	The primary benefit of the rule is a reduction in XRAY utilization. In the impact analysis, the rule recommended an XRAY in 80% of the patients. This was similar to the XRAY rate recommended in the validation cohort (77.6%). There was a potential reduction in XRAY utilization of 18.7%, 95% CI (15, 22.9%) comparing the before and after cohorts. However, the actual reduction was only 6%. The authors considered a 9% XRAY reduction to be clinically relevant.
What are the risks of applying the rule to my patients?	The primary risk of use of the rule is missing a fracture. There was a 4.5% (n=8) rate of missed fractures and a 2.3% (n=4) rate of clinically significant missed fractures.

CLINICAL BOTTOM LINE

BACKGROUND: Distal forearm fractures are one of the most common fractures in children. When imaging is performed, approximately half of patients will have a radiographically evident fracture. If patients at low risk for fracture can be identified, there is a potential to decrease XRAY utilization. The Amsterdam Pediatric Wrist Rules have been derived and externally validated. The rule has the potential to decrease radiographs by 22% without missing clinically relevant fractures (Sensitivity 95.9%, 95% CI (91.7, 98%) in the validation cohort) as well decrease ED length of stay.

CLINICAL QUESTION: In children 3-18 years of age presenting to the Emergency Department with an acute wrist injury does use of the Amsterdam Wrist Rule decrease XRAY utilization to the extent previously predicted by the prior derivation and external validation of the rule?

DESIGN/RISK OF BIAS: This was a non-randomized, before-after impact analysis of the previously derived and externally validated Amsterdam Wrist Rules in a pediatric population with acute wrist injuries. All phases of the study occurred in 4 hospitals in the Netherlands (1 academic, 3 teaching). It is unclear if any changes occurred in the management of pediatric wrist injuries in the time interval between the 2 studies and if prior utilization of the rule in the initial study could affect the rules utilization in the impact analysis.

The likelihood of a wrist injury was calculated using a mobile phone application assessing seven predictors (2 demographic, 5 physical examination). Based on the predicted risk of wrist fracture, the application provided a recommendation to obtain or not obtain radiographs. The cutoff for the recommendation was a 23% risk of fracture. It would have been helpful for the application to provide the predicted risk as well a XRAY recommendation. No training strategy was described for application implementation. However, the rule asks a series of simple questions about patient demographics and examination findings. Clinicians could deviate from the recommendation but were asked their reason for doing so. The primary outcome was the difference in the number of XRAYs in the before and after implementation cohorts. Secondary outcomes included: the number of missed clinically relevant fractures, ED length of stay, clinician compliance with the rule and patient/parent satisfaction.

PRIMARY RESULTS: 408 patients were included in the impact analysis. Fractures occurred in 44.9% (radius only: 87.7%, ulna only: 0.8%, both bones: 11.5%). The was no difference in age or fracture type comparing the Before (derivation and validation) cohort to the After (impact) cohort. The before group had a statistically higher proportion of males (59.6% vs 51.7%). This is likely irrelevant. Rule characteristics were similar comparing the impact and validation cohorts. Rule characteristics for the derivation cohort were not presented.

There was a 18.7%, 95% CI (15, 22.9%) potential reduction in XRAY utilization comparing the impact (77.9% (326/408)) and derivation plus validation cohort (98.6% (788/799)). The actual reduction in XRAY utilization was 6%. The authors considered a 9% reduction in XRAY utilization to be clinically relevant. A potential decrease in radiographs by 22.4% was predicted in the external validation cohort.

The primary risk of use of the rule is missing a fracture. There was a 4.5% (n=8) rate of missed fractures and a 2.3% (n=4) rate of clinically significant missed fractures. Physicians obtained XRAYS despite a recommendation not to in 3 of the 4 patients with clinically relevant missed fractures.

There was a statistically significant reduction in ED length of stay of 26 minutes comparing patients who did and did not have XRAYS.

RULE PERFORMANCE[1]		
	IMPACT (AFTER)(n=408)	VALIDATION (BEFORE)[2] (n=379)
Fracture Prevalence	43.1% (38.4, 48%)	44.9% (39.9, 49.9%)
Sensitivity	97.7% (94.3, 99.1%)	95.9% (91.7, 98%)
Specificity	33.2% (27.4, 39.5%)	37.3% (31, 44.1%)
Predictive Value (+) Test	52.6% (47.2, 57.9%)	55.4% (49.1, 61%)
Predictive Value (-) Test	95.1% (88, 98.1%)	91.8% (84, 96%)
Likelihood Ratio (+) Test	1.46 (1.33, 1.60)	1.53 (1.37, 1.70)
Likelihood Ratio (-) Test	0.07 (0.03, 0.18)	0.11 (0.05, 0.23)
XRAY Recommended	80% (76, 83.7%)	77.6% (73.1, 81.5%)
1. Identification of clinically relevant fractures 2. Test characteristics for the rule derivation were not presented or calculable from the data		

APPLICABILITY: The impact analysis and derivation/external validation cohorts was from 4 hospitals in the Netherlands (1 academic, 3 teaching). In the historical cohort, the academic hospital cohort served as the derivation population and the 3 teaching hospitals served as the external validation population. This likely represents a wide spectrum of disease severity and the study results are likely applicable to patients meeting the study's inclusion and exclusion criteria in similar settings. However, it is unclear how the study hospital classification corresponds to the U.S.

This is a difficulty rule to classify. It is described as an impact analysis (Level I) but did not demonstrate a clinically significant change in physician behavior (reduction in XRAY utilization). This is likely a level II rule. Level II rules are validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. Level II rules can be used in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve. Rule characteristics in this study were similar to those in the validation cohort. However, this impact analysis occurred in the same hospitals in which the rule was derived and initially validated.

AUTHOR'S CONCLUSION: "The Amsterdam Pediatric Wrist Rules are the first validated and implemented clinical decision rules in children with a suspected fracture of the distal forearm. Implementation showed that the use of the Amsterdam Pediatric Wrist Rules results in a reduction in radiographs requested and time spent at the emergency department. Although the Amsterdam Pediatric Wrist Rules could correctly identify 98% of all clinically relevant distal forearm fractures, the clinical judgment and experience of the physician still play an important part in the decision-making process for a radiographic referral in children with a trauma of the wrist."

POTENTIAL IMPACT: The study found a 18.7% potential reduction in XRAY utilization but only a 6% actual reduction in XRAY utilization. While the 6% reduction was statistically significant, it did not meet the authors definition of a 9% reduction in XRAY utilization to be clinically significant. This was somewhat misleading. The 19% potential reduction appears in both the abstract and results section. The fact that the actual reduction was only 6% only appeared in the discussion.

Use of the rule requires acceptance of the rule's definition of a clinically insignificant fractures and agreement with the rule cutoff for not recommending an XRAY in a patient with a 22% fracture risk. It would have been helpful for the application to provide the predicted risk as well a XRAY recommendation. A cutoff at a lower fracture risk would decrease the proportion of missed clinically relevant fractures at the expense of an increase in the proportion recommended XRAYS. Importantly, physicians obtained XRAYS despite the rules recommendation not to obtain them in 3 of the 4 patients with missed clinically important forearm fractures. This highlights that there is room for clinical judgment with the use of any clinical decision rule.

APPENDIX: STUDY DEFINITIONS/PROCEDURES

See also:
Slaar A, Walenkamp MM, Bentohami A, Maas M, van Rijn RR, Steyerberg EW, Jager LC, Sosef NL, van Velde R, Ultee JM, Goslings JC, Schep NW.
A Clinical Decision Rule for the Use of Plain Radiography in Children after Acute Wrist Injury: Development and External Validation of the Amsterdam Pediatric Wrist Rules.
Pediatr Radiol. 2016 Jan;46(1):50-60., PubMed ID: 26298555

FRACTURE DEFINITION
FRACTURE
A disruption of one or more cortices of the radius or ulna.
A fracture of both the distal radius and ulna, an antebrachial fracture, was recorded as one fracture.
Fissures, avulsions of bony fragments and torus (or buckle) fractures
Carpal fractures were not taken into account since the incidence in children is low
CLINICALLY IRRELEVANT FRACTURE
Fracture for which treatment or prognosis affected by the missed or delayed diagnosis
A torus fracture was considered clinically irrelevant
Fractures that received a plaster for pain regulation only were also considered clinically irrelevant.
Independently judged by a radiologist and an orthopedic trauma surgeon

PHONE FOLLOW UP QUESTIONS
REFERRAL TO CLINIC FOR REEVALUATION (ANSWER NO TO ANY)
Pain has decreased
Ability to use wrist has improved
Able to lift more than one kilogram (e.g. book or toy)
Able to push open a door
Has returned to normal daily activities (e.g. school and social activities)
Has no plan to see a doctor about wrist
ADDITIONAL QUESTIONS
Visited another physician for the wrist? If yes was XRAY obtained and/or additional treatment given

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in a population separate from the derivation set • Impact analysis with a change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

FOREARM FRACTURES:
POINT OF CARE ULTRASOUND FOR REDUCTION

In pediatric patients with a single bone forearm fracture requiring closed reduction, what is the accuracy of point of care ultrasound performed by ED physicians compared to orthopedic assessment with fluoroscopy in identifying those with and without adequate fracture reduction?

Kelsey Fawcett, M.D., Michael Mojica, M.D.

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Dubrovsky AS, Kempinska A, Bank I, Mok E.

ACCURACY OF ULTRASONOGRAPHY
FOR DETERMINING SUCCESSFUL REALIGNMENT
OF PEDIATRIC FOREARM FRACTURES

Ann Emerg Med. 2015 Mar;65(3):260-5.
PubMed ID: 25441249

STUDY DEFINITIONS	
POPULATION	Inclusion: 0-18 years old with acute (< 72hrs) forearm fracture, closed reduction required of a single bone. Performed by treating emergency physicians under procedural sedation or with the use of regional anesthesia (Bier Block) using real-time fluoroscopy Exclusion: Montaggia, Galeazzi, Intra-articular, Open Fracture, Neurovascular Impairment, Unable to provide consent Setting: Single academic Pediatric ED. 5/2012-5/2014.
TEST	Point of care ultrasound performed by ED physicians of the fracture in at least 2 planes both before and after reduction. 1. Longitudinal/Dorsal or Longitudinal/Volar = Lateral Radiograph 2. Longitudinal/Lateral = AP Radiograph
REFERENCE STANDARD	Adequate reduction <15 degrees angulation < 12 years old and 'near perfect' alignment in older children. Fluoroscopy Images post reduction: AP and lateral views. Assessed by an orthopedist
OUTCOME	1. Test Characteristics 2. Experience of physicians with ultrasound application using 5-point scale 3. Physician assessment of whether ultrasound was helpful with the reduction
DESIGN	Observational: Cross Sectional Study

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. The patients in the study constituted a representative population (100 patients, ages 0-18yo, Pediatric ED) The patient population, however, was a convenience sample. In addition, 98% of the fractures treated in the study were isolated radius fractures.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The investigators compared ultrasonography to fluoroscopy. Adequate reduction was defined as less than 15 degrees angulation in children less than 12 years old and 'near perfect' alignment in older children.
Were those interpreting the test and reference standard blind to the other results?	Yes. The ultrasound was completed prior to the fluoroscopy The orthopedic surgeon evaluating the fluoroscopy images was blinded to the ultrasound interpretations that had taken place previously.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	Yes. All patients underwent fluoroscopy to evaluate their fracture reduction after the ultrasound was performed.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

		FLUOROSCOPY		
		INADEQUATE	ADEQUATE	
ULTRA-SOUND	INADEQUATE	4	10	14
	ADEQUATE	4	82	86
		8	92	100

Prevalence (of inadequate reduction on fluoroscopy) = 8/100 = 8%
Sensitivity: 4/8 = 50%, 95% CI (21, 79%)
Specificity: 82/92 = 89%, 95% CI (81, 94%)
Predictive Value (+) Test: 4/14 = 28%, 95% CI (12, 55%)
Predictive Value (-) Test: 82/86 = 95%, 95% CI (89, 98%)
Likelihood Ratio (+) Test: (T+/D+)/(T+/D-) = (4/8)/(10/92) = 4.6, 95% CI (1.9, 11.4)
Likelihood Ratio (-) Test: (T-/D+)/(T-/D-) = (4/8)/(82/92) = 0.6, 95% CI (0.28, 1.1)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	Unclear. Overall, the study was well designed, however, it would have been beneficial to have another orthopedist evaluating the fluoroscopy images to assess inter-rater reliability. It would also have been helpful to have a more concrete definition of the term ‘near perfect’ reduction. In addition, approximately 50% of the ultrasounds were performed by only 2 of the 16 faculty members. The sensitivity was 100% in these 2 faculty and 33% for those who completed < 10 ultrasounds.
Are the study results applicable to the patient in my practice?	Yes. The patients in this study appeared to be similar to that of our population. Patient age was similar, as was the injury being studied. One major difference would be that rather than the ED physician doing the fracture reduction, most often this is done by an Orthopedist. This, however, does not mean that our ED physicians could not be responsible for the pre and post reduction point of care ultrasound.
Will the results change my management strategy?	The study will likely not change our management strategy in the immediate future. However, with more evidence for the utility of ultrasound in the Pediatric ED and the potential for it to be used in place of fluoroscopy to assess fracture realignment, it would most certainly be a practical and safe method that we would be in favor of introducing to our practice.
Will patients be better off as a result of the test?	The proposed test (ultrasonography) would expose the patient population to less radiation than the current standard of fluoroscopy. However, the study indicates that despite inadequate fracture reduction in a number of patients, the injury healed appropriately indicating that perhaps the initial intervention of reduction for a mild angulated fracture, may not be necessary.

CLINICAL BOTTOM LINE

BACKGROUND: Traditionally, fluoroscopy has been used in the Pediatric Emergency Department to evaluate for successful re-alignment of pediatric fractures. Over the last decade, point of care ultrasound has demonstrated great utility by providing rapid real time images, at the bedside, without exposing patient, family members, or healthcare workers to radiation. To date, there have only been few studies looking at the use of point of care ultrasound to evaluate realignment of pediatric forearm fractures.

CLINICAL QUESTION: In pediatric patients with a single bone, forearm fracture requiring closed reduction what are the test characteristics of point of care ultrasound performed by ED physicians compared to orthopedic assessment with fluoroscopy in determining the adequacy of fracture reduction?

DESIGN/VALIDITY: This was a well-designed cross sectional study of a convenience sample (100 patients) of pediatric patients with a single bone forearm fracture in a single Pediatric ED. There were few risks of bias. The primary concern is that only one physician each completed the interpretation of the ultrasound and fluoroscopic images for adequacy of reduction. A measure of inter-rater reliability (e.g. kappa) would be have been helpful to assess the reproducibility of the study's results. The study would have also benefited from the clear definition of a "near perfect" reduction in the post-pubertal population to determine if ultrasonographers and orthopedists were using the same definition of adequate reduction.

PRIMARY RESULTS: The sensitivity of ultrasound was poor. Only 50%, 95% CI (21, 79%) of those with an inadequate reduction on fluoroscopy were identified on ultrasound. In contrast, specificity was higher at 89% 95% CI (81, 94%) indicating that 89% of the studied patients with adequate reduction on fluoroscopy had an adequate reduction on ultrasound. The corresponding likelihood ratios were: likelihood ratio of a positive test of 4.6, 95% CI (1.9, 11.4) and a likelihood ratio of a negative test of 0.6, 95% CI (0.28, 1.1). These test characteristics indicate that point of care ultrasound is a better tool to rule in adequate fracture reduction than to rule out inadequate reduction by may not be the sufficient to guide assessment of pediatric forearm fractures realignment.

APPLICABILTY: The study would likely apply to our population. It would have been beneficial to have another orthopedist evaluating the fluoroscopy images to assess inter-rater reliability. We additionally would have liked a more concrete definition of the term 'near perfect' in the description of forearm fracture in post-pubertal children. 98% were radius fractures. It is unclear if the study's results could be generalized to single bone ulna fractures

Approximately 50% of the ultrasounds were performed by only 2 of the 16 faculty members. The sensitivity was 100% in these 2 faculty and 33% for those who completed < 10 ultrasounds. This indicates that there appears to be a learning curve. It is unclear if those with prior ultrasound experience could translate their expertise to musculoskeletal ultrasound or if training was inadequate for novice sonographers.

AUTHOR'S CONCLUSION: "Point-of-care ultrasonography can accurately assess the successful realignment of fractures of the forearm in children, but inadequate reductions should be confirmed by other imaging modalities. Ultrasonography provides clinicians the ability to safely guide fracture realignment without requiring the equipment or personnel needed for fluoroscopy, and it does not expose the patient or the staff to any radiation. Future randomized studies are needed to determine

whether this approach improves procedure time, number of attempts or successful reductions, and patient and parental satisfaction, as well as whether it can aid in the reduction of fractures in which both bones need realignment.”

POTENTIAL IMPACT: The study will likely not change our management strategy in the immediate future. More evidence is needed to determine utility of ultrasound for fracture realignment. It would most certainly be a practical and safe method that we would be in favor of introducing to our practice. Additional training and clinical experience should foster additional facility with musculoskeletal ultrasound.

FOREARM FRACTURES:
REMOVABLE SPLINT FOR TORUS FRACTURES

In children with a radiographically confirmed Buckle (torus) fracture of the distal forearm, does a removable splint when compared to casting allow improved functioning?

Eric Weinberg M.D., Adriana Manikian, M.D.
July 2006

Plint AC, Perry JJ, Correll R, Gaboury I, Lawton L.

A RANDOMIZED, CONTROLLED TRIAL OF REMOVABLE SPLINTING VERSUS CASTING FOR WRIST BUCKLE FRACTURES IN CHILDREN.

Pediatrics. 2006 Mar;117(3):691-7.
PubMed ID: 16510648

STUDY DEFINITIONS	
POPULATION	Inclusion: 6-15 years, present to ED, buckle fracture of the distal radius or ulna. A buckle fracture was defined as: compression of the bony cortex with the opposite cortex intact) Exclusion: Another fracture of the same limb requiring immobilization, fractures of both wrists, evidence of metabolic bone disease, language barrier, lived outside the hospital catchment area Setting: Single Children's Hospital ED (Canada), 8/2002-9/2003
INTERVENTION	Individually fitted plaster splint (12 layers), attached with a tensor bandage Instructions: Use the splint for comfort only, remove as desired for activities, discontinue when desired.
CONTROL	Short arm (below elbow) plaster cast Usual verbal and written cast-care instructions (e.g. avoid getting wet).
CO-INTERVENTION	Avoid contact sports until orthopedic follow-up at 21 days Phone follow up at 7, 14, 20, and 28 days: Activities Scales for Kids performance version (ASKp) answers, child's difficulty with daily living and sporting activities, amount of splint use, and difficulties with cast or splint. 6 month phone follow up and hospital charts reviewed to determine re-fractures.
OUTCOME	Primary Outcome: Change in mean functional activity as measured by the Activities Scale for Kids (modified) (ASKp) at 2 and 4 weeks (See Appendix) Other Outcomes: ASKp score at days 7, 20, and 28 post-injury Change from baseline in ASKp at days 7, 14, 20, and 28 Pain: Visual analog pain score Ability to perform daily and sporting activities throughout the study: Likert scale Length of splint use Parent and child satisfaction at day 28 Re-fracture at 6 months
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Children were randomized to two groups: removable plaster splint vs short arm cast for 3 weeks. Patients were randomized via computer and then by envelope.
Was randomization concealed?	No. Randomization was initially concealed using an opaque envelope until the research assistant or ED staff applied the intervention.
Were patients in the study groups similar with respect to known prognostic factors?	No. Table 1: There are several apparent differences between the two groups, although the authors state that enrolled patients were similar. The cast group had more patients with moderate fractures. However, a subgroup analysis that found similar results in the moderate fracture group. Another difference is a higher initial ASKp score in the cast group (97 vs 93). The higher initial ASKp score in the cast group could cause a significantly larger (and possibly false) decrease in the ASKp score at follow up. A third difference is a larger initial VAS score with the splint group, which could falsely elevate the VAS scores at follow up. However, this difference is not clinically significant (for VAS scores a minimum difference of 13 is considered clinically significant).
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Patients, clinicians, and outcome assessors were aware of group allocation. Outcome assessors were aware of group allocation because the questions they asked were individualized to the intervention. This could introduce potential bias when gathering data. In addition, the patients and parents also functioned as outcome assessors.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	For the most part. 3/57 (5.2%) patients in the splint group and 2/56 (3.6%) patients in the cast group were lost to follow up. At the 21-day clinic follow up 6/42 (14.3%) patients in the splint group and 5/45 (11.1%) patients were lost to follow up. Also, 8/42 (19%) and 4/45 (8.9%) patients were lost to f/u at 6 mos. The authors reviewed patient's charts to see determine is any of the patients had visited the hospital for complications (the hospital is the only hospital in the catchment area with a pediatric orthopedic program).
Were patients analyzed in the groups to which they were randomized?	Yes. The primary analysis was an intention to treat analysis. There were no patients who did not receive the intended intervention.
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N=113 enrolled, 87 included in the primary analysis
100% radius fracture,
8% radius and ulna fracture

Primary Outcome: ASKp Score at Day 14 (Table 2)
Higher score = better function. Median (IQR)
Splint group: 93.77, 95% CI (87.26, 99.15)
Cast group: 89.29, 95% CI (82.33, 95.69)
Median Difference: 2.97, 95% CI (0.00, 6.90)

Secondary Outcomes: ASKp (Table 2)
ASKp at Day 7, 20, 28:
No significant difference change in ASKp from baseline:
Splint group with significantly higher improvement at days 14 and 20.

Secondary Outcomes: Pain (Table 2)
VAS score: No significant difference at any point

Secondary Outcomes: Activities (Table 3)
Bathing/Showering D7,14, 20: Splint > Cast (sig)
Return to sports play D20, 28: Splint > Cast (sig)

Secondary Outcomes: Complications
Return to ED: Cast (5) vs Splint (0)
No re-fractures in either group.

Secondary Outcomes: Splint Usage
Splint group: 13.6 ± 6 days (for at least once each day)
Cast group: 21 days

Secondary Outcomes: Satisfaction (Splint preferred)
Splint group: Parents (85%), Patients (95%)
Cast group: Parents (52%), Patients (78%)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The confidence interval for the median difference in the primary outcome of 2.97 had a 95% confidence interval of (0.00, 6.90). This is wide (imprecise). While this was a statistically significant difference, the authors defined a clinically significant difference as 15 in their sample size determination.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	The study patients are similar to our patients. Only difference is non-English speaking which should not alter results.
Were all patient important outcomes considered?	The authors were fairly exhaustive in accounting for all outcomes (ASKp scores, VAS scores, activity functioning, re-fracture rates).
Are the likely treatment benefits worth the potential harm and costs?	The likely benefits (increase in daily functioning, less healthcare usage) seem to outweigh the risk (risk of re-fracture). Zero patients in either group had documented re-fractures. However, the authors would have need approximately 5,000 patients to detect a difference of 1% in re-fracture rates.

CLINICAL BOTTOM LINE

BACKGROUND: Buckle fractures (also known as torus fractures) are a common form of wrist fracture that is specific to pediatric patients' due to the relative flexibility of growing bones. There is great variability in the treatment of buckle fractures, with some physicians using immobilization via casting for several weeks, while others prefer removable splints.

CLINICAL QUESTION: In children with a radiographically confirmed buckle (torus) fracture of the distal forearm, does a removable splint allow improved functioning when compared to casting?

DESIGN/VALIDITY: This was a well-designed randomized clinical trial including 87 patients in the primary analysis. The article compared the level of functioning at two weeks (using a self-reported tool called the ASKp) with patients randomized to either casting for 3 weeks or a removable splint. The primary validity concern is the proportion who were lost to follow up or had missing study data.

PRIMARY RESULTS: The authors found a statistically significant difference in the primary outcome. Patients in the removable splint group had higher ASKp score (better function) at 14 days compared to the cast group (Splint group: 93.77, Cast group: 89.29, Difference: 2.97, 95% CI (0.00 to 6.90). While this was a statistically significant difference, the authors defined a clinically significant difference as 15 in their sample size determination.

For secondary outcomes, patients reported significantly less difficulty with activities of daily living with the removable splint, less return visits to the ED and a higher preference for the splint regardless of study group. There were no patients sustaining a re-fracture in the study. However, the study was underpowered to determine a difference in this rare outcome.

APPLICABILITY: The study's results appear to be generalizable to pediatric patients with distal forearm torus fractures meeting the study's inclusion and exclusion criteria.

AUTHOR'S CONCLUSION: "Children treated with removable splinting have better physical functioning and less difficulty with some activities than those treated with a cast, with no difference in their level of pain. The use of removable splinting may reduce the need for follow-up visits and, as a result, health care costs. We recommend the use of removable splints in the treatment of this common injury."

POTENTIAL IMPACT: This was a well-done study that suffers somewhat from a fall sample size, missing data due to incomplete record keeping by parents and some loss to follow up. The results however seem encouraging with removable splinting resulting in quicker return to function and potentially less need for follow up. Larger studies should confirm these results. A change in management would require collaboration with our pediatric orthopedic colleagues.

APPENDIX: PRIMARY OUTCOME (ASKp)

ACTIVITIES SCALE FOR KIDS (MODIFIED) WEB LINK
Self-report measure of physical disability.
5-15 years experiencing limitations in physical activity due to musculoskeletal disorders.
Contains 30 items that are aggregated into an overall summary score.
The ASKp measures what the child "did do" during the previous week.

Young NL, Williams JI, Yoshida KK, Wright JG.
Measurement Properties of the Activities Scale for Kids
J Clin Epidemiol. 2000 Feb;53(2):125-37., PubMed ID: 10729684

SEPTIC ARTHRITIS:
DECISION RULE DERIVATION (KOCHER)

In children with an acutely “irritable hip” for which there is a concern for septic arthritis, do clinical and laboratory findings adequately distinguish between septic arthritis and transient synovitis?

Michael Mojica, M.D.
June 2017

Kocher MS, Zurakowski D, Kasser JR

DIFFERENTIATING BETWEEN SEPTIC ARTHRITIS AND TRANSIENT SYNOVITIS OF THE HIP IN CHILDREN: AN EVIDENCE-BASED CLINICAL PREDICTION ALGORITHM

J Bone Joint Surg Am. 1999 Dec;81(12):1662-70.
PubMed ID: 10608376

STUDY DEFINITIONS	
POPULATION	Inclusion: Acutely irritable hip for which the differential diagnosis involved transient synovitis and septic arthritis. Joint fluid aspirate for cell count, gram stain or culture, ESR, peripheral WBC and blood culture obtained. Exclusion: Immunocompromised, renal failure, neonatal sepsis, postoperative infection of the hip, proximal femoral osteomyelitis, later development of rheumatologic or Legg-Calve-Perthes disease Exclusion of Equivocal Cases: Joint fluid WBC < 50,000 cells/mm^3 with negative cultures and managed with 1. Arthrotomy and intravenous antibiotics OR 2. Intravenous antibiotics alone Setting: Single Children's Hospital, 1979-1996
INTERVENTION	Possible predictors included: Patient: Age, gender History: Fever, chills, trauma, concurrent or recent infection, recent antibiotics, weight-bearing status, temperature on presentation (Fever defined as Oral temperature > 38.5 C in the week prior) Laboratory Peripheral Blood: ESR, CBC with differential, Blood culture, Laboratory Joint Fluid: Gram-stain, cell count with differential, aspirate culture Radiology: Evidence of effusion on XRAY
CONTROL	Septic Arthritis: True Septic Arthritis and Presumed Septic Arthritis "True" Septic Arthritis: 1. Positive joint fluid culture OR 2. Joint fluid WBC ≥ 50,000 cells/mm^3 per AND a positive blood culture. Presumed Septic Arthritis: Joint fluid WBC ≥ 50,000 cells/mm^3 with negative joint and blood cultures Transient Synovitis: Joint fluid WBC < 50,000 cells/mm^3 AND negative cultures, AND resolution of symptoms without antibiotics.
OUTCOME	Rule Characteristics
DESIGN	Observational: Retrospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes and No. The most commonly considered predictors were included in the analysis. However, details of the physical examination other than weight bearing status obtained by history were not included.
Were all important predictors present in significant proportion of the study population?	Yes and No. The proportion of patient with each of the dichotomous predictors is presented in Table 1 comparing those with septic arthritis to those with transient synovitis. However, for continuous variables such as WBC and ESR the mean values in each group are compared and not the proportion of patients with the predictor.
Were the outcome event and predictors clearly defined?	Yes. The predictor definitions were clearly defined and for the most part objective. The outcomes of septic arthritis and transient synovitis were also clearly defined. Septic arthritis included both “true” septic arthritis and “presumed” septic arthritis. Unclear cases of septic arthritis were excluded.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Unclear. This was a retrospective cohort (chart review) and those reviewing the charts may have known the outcome prior to abstracting the predictor variables. However, the majority or the predictors and the outcome are objective laboratory data such as the joint aspirate cell count, aspirate culture and blood culture. Lack of blinding, if it occurred, would be unlikely to affect the study’s results.
Was the sample size adequate (including an adequate number of outcome events)?	Yes. In general, logistic regression requires 10 outcomes for very variable included in the final model. The final model included 4 variables and there were 82 patients with septic arthritis.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)
HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? How precise was this measurement? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

N = 168,
Mean age 5.6 years
Septic Arthritis: 82 (True: 38, Presumed: 44)

BACTERIOLOGY	
Staphylococcus aureus	58%
Streptococcal pneumoniae	16%
Haemophilus influenza*	13%
Neisseria Meningitides	8%
Group A Streptococcus	5%
*Type not provided. All cases were prior to 1988	

Transient Synovitis: 86
The precision of the predictors is low. The small number of patients with septic arthritis resulted in very large confidence intervals around the adjusted odds ratios of the independent predictors from the regression analysis.

INDEPENDENT PREDICTORS	ADJUSTED ODDS RATIO (95% CI)	LIKELIHOOD RATIO
History of fever	38.6 (10.8, 137.0)	29.5
History of non-weight bearing	24.3 (5.6, 85.3)	10.7
ESR > 40 mm/hour	25.9 (6.5, 112.6)	19
WBC > 12,000 cells/mm^3	14.4 (4.0, 51.5)	14

CLINICAL DECISION RULE: PERFORMANCE	
NUMBER PREDICTORS	SEPTIC ARTHRITIS (%)
0	0.2 %
1	3.0 %
2	40.0 %
3	93.1 %
4	99.6 %
AUR (Area under the receiver operating characteristic curve) = 0.96	

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?
Unclear. The rule does not specify a course of action. However, in the discussion the authors suggest management options based on the probability of septic arthritis.
WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?
No. There was no internal statistical validation of the rule.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

At what level of development is this rule? How can it be applied?	☐ I ☐ II ☐ III ■ IV This is a level IV clinical decision rule. A level IV rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. A level IV rule requires further validation before it can be applied clinically.
Does the rule make clinical sense?	Yes. The predictors in the rule include history and laboratory findings suggestive of an infection localized to the hip.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. Inter-rater reliability of the rule predictors was not provided. While the peripheral WBC and ESR are objective laboratory data, a history of fever or refusal to bear weight may be open to interpretation.
Is the rule applicable to the patients in my practice?	Unclear. The setting of the study was a single children's hospital. It is likely the study's results are generalizable to similar settings. However, little demographic information on the study population is provided other than their age, gender. In addition, the study spanned 17 years and 29% of patient had current vaccine preventable infections.
Will the rule results change my management strategy?	Yes. The use of the 4-predictor rule would simplify the assessment of septic arthritis and the "Kocher" rule has been used clinically for many years.
What are the benefits of applying the rule to my patients?	The primary benefit of applying the rule is to identify those who have septic arthritis so that appropriate management can occur in a timely fashion. In addition, patients without septic arthritis could be spared surgery and antibiotics and could possibly be discharge and followed closely as outpatients.
What are the risks of applying the rule to my patients?	As with any rule there is a potential for misclassification. Those with septic arthritis could be missed with serious sequelae and those with transient synovitis could receive unnecessary interventions.

CLINICAL BOTTOM LINE

BACKGROUND: The differential diagnosis of the child with hip pain is extensive and can divided into infectious (septic arthritis) para-infectious (transient synovitis), traumatic (slipped capital femoral epiphysis), rheumatologic (juvenile immune arthritis) and other causes (Legg-Calve-Perthes disease). In the febrile patient with symptoms localized to the hip, septic arthritis requires urgent identification. The blood supply to hip is tenuous and increased pressure in the hip capsule can lead to decreased blood flow and subsequent ischemic necrosis and growth arrest. Early diagnosis and treatment with operative drainage and antibiotics is essential to prevent complications. Unfortunately, transient synovitis which is self-limited and without significant complications can present similarly to septic arthritis. The ability to distinguish between septic arthritis and transient synovitis is essential.

CLINICAL QUESTION: In children with an “irritable hip” for which there is a concern for septic arthritis, do clinical and laboratory findings adequately distinguish between septic arthritis and transient synovitis?

DESIGN/RISK OF BIAS: This was a well-designed, retrospective cohort study to assess the accuracy of clinical and laboratory findings in identifying septic arthritis. 168 patients were included in the primary analysis. 82 (49%) of which had septic arthritis. Septic arthritis was clearly defined and was a composite of “true” septic arthritis and “presumed” septic arthritis (see study definitions). To avoid selection bias, those with equivocal diagnoses of septic arthritis were excluded. There were no major risks of bias identified.

PRIMARY RESULTS: 13 variables had statistically significant association with septic arthritis in the univariate analysis. However, there was significant overlap of these variables in those with and without septic arthritis limiting the diagnostic accuracy of any single variable. The logistic regression analysis identified 4 variables that were independent predictors of septic arthritis. These 4 variables were: history of fever, history of non-weight bearing, peripheral WBC > 12,000 cells/mm3 and an ESR > 40 mm/hour. The 4-predictor rule had a very high diagnostic accuracy as indicated as an area under the receiver operating characteristic curve of 0.96.

INDEPENDENT PREDICTOR	ADJUSTED ODDS RATIO (95% CI)	LIKELIHOOD RATIO
History of fever	38.6 (10.8, 137.0)	29.5
History of non-weight bearing	24.3 (5.6, 85.3)	10.7
ESR > 40 mm/hour	25.9 (6.5, 112.6)	19
WBC > 12,000 cells/mm^3	14.4 (4.0, 51.5)	14

There was a direct relationship between number of predictors and the probability of septic arthritis. However, the test characteristics of the individual predictors and based on the number of predictors were not presented. One of the problems with a composite rule that is based on the number or predictors present is that it assumes that each predictor has equal weight. This was not the case. In the regression analysis, the adjusted odds ratio for history of fever (aOR 38.6) was 1.5 times larger than the odds ratio for the nearest predictor (ESR > 40 mm/hour, aOR 25.9) and 2.7 times larger than the odds ratio for the lowest predictor (WBC > 12,000 cells/mm^3, aOR 14.4). The AUR (Area under the receiver operating characteristic curve) was 0.96.

CLINICAL DECISION RULE: PERFORMANCE	
NUMBER PREDICTORS	SEPTIC ARTHRITIS (%)
0	0.2 %
1	3.0 %
2	40.0 %
3	93.1 %
4	99.6 %
AUR (Area under the receiver operating characteristic curve) = 0.96	

The impact of the use of the rule on resource utilization is unclear. The rule does not specify a course of action. However, in the discussion, the authors suggest management options based on the probability of septic arthritis.

APPLICABILITY: The setting of the study was a single, children's hospital. It is likely the study's results are generalizable to similar settings. However, little demographic information on the study population is provided other than their age and gender. In addition, the study spanned 17 years and included 29% of patients with currently vaccine preventable infections. The epidemiology of disease has changed since that time and it is unclear if the rule performance would be similar with our current mix of pathogens. Finally, the reproducibility of the non-laboratory parameters was not assessed.

This is a level IV clinical decision rule. A level IV rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. A level IV rule requires further validation before it can be applied clinically.

AUTHOR'S CONCLUSION: "Although several variables differed significantly between the group that had septic arthritis and the group that had transient synovitis, substantial overlap in the intermediate ranges made differentiation difficult on the basis of individual variables alone. However, by combining variables, we were able to construct a set of independent multivariate predictors that, together, had excellent diagnostic performance in differentiating between septic arthritis and transient synovitis of the hip in children."

POTENTIAL IMPACT: This study is still quoted as the "Kocher rule' nearly 20 years after its publication. Since that time other potential predictors such as MRI, ultrasound findings and newer acute phase reactants such a C-reactive protein have become available. The primary benefit of applying the rule(s) is to identify those who have septic arthritis so that appropriate management can occur in a timely fashion. In addition, patients without septic arthritis could be spared surgery and antibiotics and could possibly be discharge and followed closely as outpatients. As with any rule there is a potential for misclassification. Those with septic arthritis could be missed with serious sequelae and those with transient synovitis could receive unnecessary treatment. However, the rule characteristics required to determine the rate of misclassifications was not provided.

A subsequent retrospective validation of the Kocher rule found that the area under the receiver operating characteristic curve was 0.79 (compared to 0.96 for the Kocher rule derivation) and that patients with all 4 of the predictors had a 59.1% risk of septic arthritis (compared to 99.6% for the Kocher rule derivation) (Luhman, J Bone Joint Surg AM, PubMed ID: 15118038). A prospective validation of the Kocher rule found that a CRP > 2.0 mg/dl was a stronger predictor of all but a history of fever (Caird, J Bone Joint Surg AM, PubMed ID: 16757758, 2006).

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

PAINFUL PROCEDURES

1. Analgesia: Dilaudid for Severe Pain: Annals M. 2011
2. Analgesia: Pediatric Fracture Pain: Ann Emerg Med. 2009
3. Analgesia: IN Fentanyl/Ketamine: Annals EM 2015
4. Analgesia: IN Fentanyl/Ketamine: JAMA Peds 2019
5. Analgesia: Morphine Dosing (Adult): Annals EM 2007
6. Analgesia: Topic Lidocaine for Oral Ulcers: Ann EM. 2014
7. Sedation: Adverse Event Risk Factors: JAMA Peds 2017
8. Sedation: Ketamine Adverse Events: Annals EM. 2009
9. Sedation: Ketamine Route: Ann Emerg Med. 2006
10. Sedation: Ondansetron with Ketamine: Annals EM 2008
11. Sedation: Fasting Status (Prospective) Annals EM 2003
12. Sedation: Fasting Status (Retrospectiv) Annals EM 2004

ANALGESIA:
DILAUDID FOR SEVERE PAIN (ADULTS)

In adult patients with severe, acute pain in the Emergency Department can a regimen of 1 mg of Hydromorphone (Dilaudid) initially followed by an additional 1 mg if needed at 15 minutes when compared to “Usual care” reduce requests for additional pain medication at one hour?

Kelly Cleary, M.D., Deborah Levine, M.D.
December 2011

Chang AK, Bijur PE, Gallagher EJ.

RANDOMIZED CLINICAL TRIAL COMPARING THE SAFETY AND EFFICACY OF A HYDROMORPHONE TITRATION PROTOCOL TO USUAL CARE IN THE MANAGEMENT OF ADULT EMERGENCY DEPARTMENT PATIENTS WITH ACUTE SEVERE PAIN.

Ann Emerg Med. 2011 Oct;58(4):352-9.
PubMed ID: 21507527

STUDY DEFINITIONS	
POPULATION	Inclusion: 21-64 years of age, presenting to ED with acute pain (< 7 days), sufficient severity for intravenous opioid use as per ED attending judgment Exclusion: Patients whose ED attending physicians were part of the research group (not blinded to study hypothesis), allergy to Hydromorphone or Morphine, systolic BP < 90 mm Hg, room air oxygen saturation < 95%, alcohol or other drug intoxication, use of other opioids in past 7 days, use of a monoamine oxidase inhibitor, weight less than 100 pounds, pregnancy, presence of a chronic pain syndrome (e.g. sickle cell disease, fibromyalgia). Setting: Single academic, urban medical center. 10/2008-5/2009
INTERVENTION	1+1 Hydromorphone Group: Initial dose of 1 mg intravenous hydromorphone. Asked at 15 minutes “Do you want more pain medication?” If answered YES group received an additional dose of 1 mg of intravenous hydromorphone.
CONTROL	Usual Care Group: Initial type and dose of an intravenous opioid at discretion of ED attending. Asked at 15 minutes “Do you want more pain medication?” If answered YES, attending physician notified and additional analgesic at their discretion
CO-INTERVENTION	If either group responded NO to the question at 15 minutes, additional medication could be provided if requested later.
OUTCOME	Primary Efficacy Outcome: Proportion successfully treated: 1. Declined additional pain medication at 15 minutes OR 2. Accepted additional pain medication at 15 minutes but declined additional pain medication at 60 minutes Secondary Efficacy Outcome: Change in numeric rating scale pain score from baseline to 15 and 60 minutes Safety Outcomes: Need for naloxone, desaturation < 95%, hypoventilation, hypotension, nausea, vomiting, pruritus.
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized by an online random-number generator.
Was randomization concealed?	Yes. The randomization was concealed. Assignments were placed in sealed opaque envelopes.
Were patients in the study groups similar with respect to known prognostic factors?	At baseline, there were significant differences in gender, weight, location of pain, and nausea. A logistic regression analysis was used to control for these factors.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Unclear if patients were blinded to the medication they were receiving. They were likely unaware of study group and medication received. Physicians were not blinded. However, they did not know the study hypothesis or outcomes.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Follow-up was complete. The study was complete at 60 minutes for each patient enrolled.
Were patients analyzed in the groups to which they were randomized?	Yes. Patients were analyzed both per protocol and by intention to treat analysis.
Was the trial stopped early?	No. The trial was not stopped early.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Hydromorphone Group: N = 167 intention to treat, N = 156 per protocol

Usual Care Group: N = 171 both ITT and per protocol

Abdominal Pain: 61.5%
Pain Score = 10: 55.9%. Pain Score ≥ 9: 71.5%

Primary Outcome: Percent Successful Treatment

SUCCESSFUL TREATMENT: INTENTION TO TREAT ANALYSIS			
	SUCCESSFUL TREATMENT		
	YES	NO	
1+1 HYDROMORPHONE	145	22	167
USUAL CARE	131	40	171
	276	62	338

Absolute Risk (1+1 Hydromorphone): 145/167 = 86.8%
Absolute Risk (Usual Care): 131/171 = 76.6%
Absolute Risk Difference: 86.8% – 76.6% = 10.2%, 95% CI (2, 18.3%)

SUCCESSFUL TREATMENT: PER PROTOCOL ANALYSIS			
	SUCCESSFUL TREATMENT		
	YES	NO	
1+1 HYDROMORPHONE	144	12	156
USUAL CARE	131	40	171
	275	53	323

Absolute Risk (1+1 Hydromorphone): 144/156 = 92.3%
Absolute Risk (Usual Care): 131/171 = 76.6%
Absolute Risk Difference: 92.3% – 76.6% = 15.7%, 95% CI (7.9, 23.3%)

Logistic Regression Analysis: Control for sex, location of pain, and nausea did not change the magnitude or statistical significance of the difference.

Secondary Outcomes
In the per protocol analysis, there was a statistically and clinically significant (>10%) decrease in those requesting additional medication in the Hydromorphone group at 15 and 60 minutes. This was not true in the intention to treat analysis.

Adverse Events:
No was no significant differences.
The most common adverse events were pruritus, nausea and vomiting.
No patients required Naloxone.

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?
A 10% difference was defined as clinically significant by the authors in the sample size determination. The risk differences were clinically significant by the authors criteria. The confidence intervals for both absolute risk differences indicate a statistically significant difference.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. Though the study was done in adults, the patient demographics were similar to our young adult population.
Were all patient important outcomes considered?	Yes. The study looked at successful treatment of pain (declining pain meds at 15 minutes or 60 minutes) the change in numeric pain scales as well as adverse events.
Are the likely treatment benefits worth the potential harm and costs?	<u>Number Needed to Treat (NNT)</u> NNT= 1/ARD = 1/(0.102) = 9.8 (intention to treat analysis) NNT= 1/ARD = 1/(0.157) = 6.3 (per protocol analysis) Based on the ITT analysis, for every 9.8 patients treated with 1+1 Hydromorphone 1 additional patient would be considered a treatment success when compared to usual care. For the per protocol analysis substitute 6.3 in the above sentence. This study did not show a statistically significant difference in the safety profiles of either regimen.

CLINICAL BOTTOM LINE

BACKGROUND: The optimal regimen of analgesics for patients with moderate–severe pain in the emergency department is unknown. A protocol for addressing patients pain at a pre-specified interval and standardization the medication, dosing and frequency may improve the need for additional medication.

CLINICAL QUESTION: In adult patients with severe, acute pain in the Emergency Department can a regimen of 1 mg of Hydromorphone (Dilaudid) initially followed by an additional 1 mg if needed at 15 minutes when compared to “usual care” reduce requests for additional pain medication at one hour?

DESIGN/VALIDITY: The was a well-designed randomized controlled trial including 338 patients in the primary intention to treat analysis. The study would have benefited from a better description of the cause of pain. While the most common cause in both study groups was abdominal pain, the non-abdominal pain causes are simply listed as other.

PRIMARY RESULTS: There was a clinically and statistically significant difference in successful treatment favoring the 1 + 1 hydromorphone group when compared to usual care group (primarily morphine at treating physician discretion). Absolute Risk Difference (Intention to treat analysis): (1 + 1 Hydromorphone – Usual Care) = 10.2%, 95% CI (2, 18.3%). Absolute Risk Difference (Per protocol analysis): (1 + 1 Hydromorphone – Usual Care) = 15.7%, 95% CI (7.9, 23.3%). The 1 + 1 hydromorphone group received more medication than the usual care group with a mean total dose 12.6 versus 9.0 morphine equivalents. For every 9.8 patients (intention to treat) or 6.3 patients (per protocol) treated with 1+1 Hydromorphone 1 additional patient would be considered a treatment success when compared to usual care. There was no difference in adverse events.

APPLICABILITY: The applicability of the study to other settings where “usual care” is not the same is unknown. This study is likely generalizable to our young adult population not meeting study exclusion criteria. Dosing adjustments would be required for younger patients.

AUTHOR’S CONCLUSION: “When analyzed per protocol or with the more conservative intention-to-treat analysis, the 1 1 hydromorphone protocol is statistically and clinically more efficacious than usual care. Safety profiles were similar in both groups.”

POTENTIAL IMPACT: There are some issues in implementing this approach. The first is that 7% of the patients in the study group did not receive additional medication as directed by the protocol highlighting the difficulty of frequent pain assessment and analgesic administration in a busy emergency department setting. The second is that 8% that did receive the study intervention still required additional medications at 1 hour.

ANALGESIA:
PEDIATRIC FRACTURE PAIN

In patients 4-18 years of age that are discharged from the ED with simple upper extremity fractures (radius,ulna, humerus) not requiring reduction does Ibuprofen when compared to Acetaminophen with Codeine provide superior analgesia defined as the less frequent use of a rescue medication?

Vaishali Shah, M.D., Ee Tay, M.D.
September 2009

Drendel AL, Gorelick MH, Weisman SJ, Lyon R, Brousseau DC, Kim MK.

A RANDOMIZED CLINICAL TRIAL OF IBUPROFEN VERSES ACETAMINOPHEN WITH CODEINE FOR ACUTE PEDIATRIC ARM FRACTURE PAIN.

Ann Emerg Med. 2009 Oct;54(4):553-60.
PubMed ID: 19692147

STUDY DEFINITIONS	
POPULATION	Inclusion: 4-18 years, fracture of the radius, ulna, or humerus Exclusion: Isolated posterior fat pad of the elbow, required reduction or manipulation in the ED, open fractures. > 60 kg, preferred tablet medications, > 12 hours after injury, History of developmental delay, gastrointestinal bleeding/ulceration, bleeding disorder, history of a low platelets, kidney disease, uncontrolled chronic disease, regular use of or allergy to Acetaminophen, Ibuprofen, or Codeine. parents unable to understand English, inaccessible by telephone. Setting: Single Children's Hospital ED, 8/2003-9/2007
INTERVENTION	Ibuprofen: 10 mg/kg per dose Q4-6H (max 4 doses/24hours)
CONTROL	Acetaminophen/Codeine (1 mg/kg of codeine Q4-6H (max 4 doses/24hours)
CO-INTERVENTION	1. Discretionary use of analgesics in the ED. 2. Splinted by ED personnel: fiberglass or plaster with elastic bandage 3. Discharged with a sling and written splint care instructions 4. Use of rest, ice, compression, and elevation. 5. Follow-up with an orthopedist recommended in 5-7 days 6. Parents advised to notify the investigators if pain treatment was inadequate
OUTCOME	Primary Outcome: Use of the rescue medication (alternate study medication) Parents were instructed to give the rescue medicine for inadequate pain relief (pain score ≥ 3) 1 hour after dosing of the study medication. Secondary Outcomes: Pain score (modified Bieri Faces Pain Scale): awakening, bedtime, prior to and 1 hour after analgesic given. Scores: Daily, total median, maximum/ minimum, change pre/post medication. Function: whether play, school, sleep, eating affected by pain each day (diary) Tolerability (adverse events) Repeated fracture at same site or fracture nonunion Parent satisfaction
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized in groups of 10 by a random-number table assigned by the pharmacist.
Was randomization concealed?	The two medications were similar in texture, color, and volume but not taste. Though not explicitly stated, it does not appear that there was an opportunity to bias patient allocation into study groups.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. See Table 1. The study groups were similar in terms of demographics, type of fracture, and pain scores. Only 2 children at discharge had pain scores greater than 3, making it less likely to affect home treatment options.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The treating physician, patient, parent and all researchers were blinded to medication assignment until completion of the study. The parent and investigators were unblinded only if pain relief were deemed inadequate by the parent after the rescue medication was used. Only 3% of parents believed their child knew the assigned medication and only 36% of parents successfully guessed the assigned study medication at study completion.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. 75% completed and mailed the pain dairy. For those patients who completed and were lost to follow-up, there was no difference in age, sex, race, ethnicity, weight or fracture type.
Were patients analyzed in the groups to which they were randomized?	Yes. The authors present both an intention to treat analysis and per-protocol analysis.
Was the trial stopped early?	No. The trial was not stopped early.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 234 (Acetaminophen/Codeine: 116, Ibuprofen: 128)

Treatment Failures: Use of Rescue Medications
Absolute Risk: Ibuprofen: 20.3%
Absolute Risk: Acetaminophen/Codeine: 31.0%
Risk Difference: 10.7%; 95% CI (-0.02, 21.6%).
Not significant for the per protocol analysis as well
A 15% difference was considered clinically significant by the authors in their sample size determination.

Functional Outcomes.
There were a significantly lower number of children using Ibuprofen that had play and eating affected by pain

Adverse Effects
Ibuprofen: 29.5%
Acetaminophen with Codeine: 50.9%
Risk Difference 18.5%, 95% CI (9.1, 33.7%)

Patients receiving Acetaminophen with Codeine had significantly higher rates of nausea and vomiting (Table 3)

Patient Satisfaction
Children were more satisfied with Ibuprofen versus Acetaminophen with Codeine
Risk Difference 18.5%, 95% CI (7.3, 29.6%).

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See confidence intervals above

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Yes. The demographic characteristics and setting are similar to our population.
Were all patient important outcomes considered?	Yes. Most clinically important outcomes were considered. Parents administered the pain medications at their discretion, which may have affected clinical outcomes. It would have been helpful to present the response to rescue medications.
Are the likely treatment benefits worth the potential harm and costs?	Yes, Ibuprofen had fewer adverse effects and greater patient satisfaction. The authors found no difference between the two groups in the need for rescue medication use.

CLINICAL BOTTOM LINE

BACKGROUND: The optimal outpatient analgesic for pediatric patients with fractures not requiring reduction is not well studied. Studies in other conditions that cause pediatric pain have shown Ibuprofen to be both safe and effective. Studies in adults with fractures have come to the same conclusion.

CLINICAL QUESTION: In patients 4-18 years of age that are discharged from the ED with simple upper extremity fractures (radius, ulna, humerus) not requiring reduction does Ibuprofen when compared to Acetaminophen with Codeine provide superior analgesia defined as the less frequent use of rescue medication?

DESIGN/VALIDITY: The was a well-design, randomized clinical trial that included 244 patients in the primary intention to treat analysis. There were no major validity concerns.

PRIMARY RESULTS: The proportion of treatment failures for Ibuprofen (20.3%) was lower than for Acetaminophen with Codeine (31.0%), though this difference was not statistically significant. (10.7%, 95% CI (-0.2, 21.6%). It would have been helpful to assess the efficacy of the rescue medication given. There were a significantly lower number of children using ibuprofen that had play and eating affected by pain. Adverse events such as nausea, vomiting, and drowsiness occurred in 29.5% of the Ibuprofen group, compared with 50.9% of those receiving the Acetaminophen-Codeine (Risk Difference: 18.5%, 95% (9.1, 33.7%)).

APPLICABILITY: The study's results should be generalization to children with fractures meeting the study's inclusion and exclusion criteria.

AUTHOR'S CONCLUSION: "In conclusion, ibuprofen was at least as effective as acetaminophen with codeine in providing outpatient analgesia for children with arm fractures not requiring reduction. There was no significant difference in analgesic failure and pain scores, but children receiving ibuprofen had better functional outcomes; specifically, play. Children receiving ibuprofen had significantly fewer adverse effects, and both children and parents were more satisfied with ibuprofen. Ibuprofen is preferable to acetaminophen with codeine for outpatient treatment of children with uncomplicated arm fractures."

POTENTIAL IMPACT: There was no statistically of clinically significant difference in the need for rescue medication between Ibuprofen and Acetaminophen and Codeine. There were a significantly lower number of children using ibuprofen that had play and eating affected by pain. In addition, Ibuprofen use was associated with fewer adverse events and higher patient satisfaction.

NOTE: CODEINE USE IN CHILDREN 2016: There is substantial genetic variability in the activity of the responsible hepatic enzyme. Individual patient response to codeine varies from no effect to high sensitivity. Drug surveillance has documented the occurrence of unanticipated respiratory depression and death after receiving codeine in children. Multiple organizations and regulatory bodies, including the World Health Organization, the US Food and Drug Administration, and the European Medicines Agency, have promulgated stern warnings regarding the occurrence of adverse effects of Codeine in children and are considering a declaration of a contraindication for the use of Codeine for children as either an analgesic or an antitussive.

ANALGESIA:
INTRANASAL FENTANYL VS KETAMINE (PICHFORK)

Is intranasal Ketamine non-inferior to intranasal Fentanyl for treating moderate to severe pain in children with isolated limb injuries?

Alexis Pankow M.D., Laura Papadimitropoulos M.D.
January 2015

Graudins A, Meek R, Egerton-Warburton D, Oakley E, Seith R.

THE PITCHFORK (PAIN IN CHILDREN FENTANYL OR KETAMINE) TRIAL: A RANDOMIZED CONTROLLED TRIAL COMPARING INTRANASAL KETAMINE AND FENTANYL FOR THE RELIEF OF MODERATE TO SEVERE PAIN IN CHILDREN WITH LIMB INJURIES.

Ann Emerg Med. 2015 Mar;65(3):248-254.
PubMed ID: 25447557

STUDY DEFINITIONS	
POPULATION	Inclusion 1. Children aged 3-13 years with weight less than 50kg 2. Isolated limb injury with moderate to severe pain (≥ 6/10) Exclusion 1. Inability to obtain consent 2. Treatment with serotonergic antidepressants 3. Prior parenteral or intranasal analgesics or opioid analgesia 4.Allergy to ketamine, fentanyl or ibuprofen 5. Aberrant nasal anatomy or acute or chronic nasal problems or nasal trauma 6. Multiple trauma, head injury with loss of consciousness, cognitive impairment 7. NOT EXCLUDED: Use of simple analgesia (Acetaminophen or Ibuprofen) Setting: 2 Australian Emergency Departments. 11/2012-2/2013.
INTERVENTION	Intranasal Ketamine (via atomizer): 1.0 mg/kg
CONTROL	Intranasal Fentanyl (via atomizer): 1.5 mcg/kg
OUTCOME	Primary Outcome: Median reduction in VAS pain rating at 30 minutes after medication administration Secondary Outcomes: Reduction in pain 15, 60 min Satisfaction Rescue analgesia Degree of sedation Adverse events
DESIGN	Interventional: Randomized Clinical Trial

ARE THE RESULTS VALID?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. The randomization was via block randomization in groups of 4. Fentanyl and ketamine were added to the syringes by pharmacists. Four syringes were prepared from each block each week. Each patient received a numbered syringe in each block.
Was randomization concealed?	Yes. The medications were placed in syringes with a volume of 1.5 ml and labeled with numbers. The medication was therefore concealed from the person administering the medication. Though not explicitly stated It appears that allocation was complete because the medications were indistinguishable.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. The Ketamine group was younger by two years but groups were similar in all other respects. See Table 1.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Both the patient/parent and the medical personal administering the medication were blinded to which medication was given. The presence of nystagmus with Ketamine could have unblinded the study. Similar studies have used dark glasses to prevent visualization of nystagmus caused by Ketamine.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Figure 1. The follow up was done during the emergency department visit but some patients dropped out of the study by need for second dose of pain medications or missing reassessments. At the primary outcome at 30 minutes 34/36 (94%) receiving Ketamine and 34/37 (92%) receiving Fentanyl were included.
Were patients analyzed in the groups to which they were randomized?	This study used an intention to treat analysis so patients. All patients were included even if they had If they required rescue medications.
Was the trial stopped early	No. One of the sites was dropped from the study for low enrollment but the study continued to completion at the primary site.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Primary Outcome:
Absolute Risk (Fentanyl) = 27/34 = 79.4%

REDUCTION IN VAS AT 30 MINUTES

	> 20 mm	< 20 mm	
FENTANYL	27	7	34
KETAMINE	28	6	34

Absolute Risk (Ketamine) = 28/34 = 82.4%
Absolute Risk Difference (Fentanyl – Ketamine) = 79.4% – 82.4% = - 3.0%, 95% CI (-16, 22%)

Adverse Events* (Table 4)
Fentanyl: 15/37 = 40.5%, 95% CI (24.8, 57.9%)
Ketamine: 28//37 = 77.8%, 95% CI (60.8, 89.9%)
Risk Difference = 77.8%–40.5% = 37.3% 95% CI (-58, 16%)

No airway adverse events recorded

No significant difference in:
Pain at 15 and 60 min
Degree of sedation
Satisfaction
Need for rescue medication

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See confidence interval for absolute risk reduction.
Confidence interval indicates that here was not a statistically significant difference in reduction in VAS score at 30 minutes

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Yes. The patients were pediatric patients with no mention of ethnic background or socioeconomic status. It is unclear whether difference in pain perceptions between varying ethnic groups would have produced different results for this study.
Were all clinically important outcomes considered?	Yes. The reduction in pain scores is important but we know that these medications will reduce pain so the adverse events are also clinically important. It would have been useful to know what was in the “other” adverse event in Table 4. There was no mention of changes in vital signs or airway interventions required.
Are the likely treatment benefits worth the potential harm and costs?	There are many adverse events associated with Ketamine. 4 patients hallucinated and 5 had “other” adverse events They did not report any significant events such as laryngospasm or requiring bag mask ventilation and those are the events that are more important to physicians. The small sample size precludes drawing conclusions regarding rare adverse outcomes.

CLINICAL BOTTOM LINE

BACKGROUND: Pediatric patients with significant injuries require analgesia. The intranasal route of administration is a fast, effective and safe way to administer these medications. Intravenous access is often difficult to obtain and can be traumatizing to many pediatric patients. Intranasal fentanyl is commonly used method of analgesia. Ketamine is used in adults as an analgesic, but no study has demonstrated its efficacy in children.

CLINICAL QUESTION: Is intranasal Ketamine not inferior to intranasal Fentanyl for treating moderate to severe pain in children with isolated limb injuries?

DESIGN/VALIDITY: This was a well-designed randomized, double-blind, intention to treat study that included 68 patients in the primary analysis. There were no major validity concerns

PRIMARY RESULTS: Approximately 80% of patients had a clinically significant reduction in pain scores at 30 minutes after administration. There was not a statistically or clinically significant difference between the two groups at 30 minutes. Absolute Risk Difference (Fentanyl – Ketamine) = 79.4% – 82.4% = -3.0%, 95% CI (-16, 22). There no statistically significant difference in pain at 15 and 60 minutes, degree of sedation, satisfaction or need for rescue medication

Patients who received Ketamine had more adverse reactions (77.8%) without any added benefit of added pain relief over Fentanyl (40.5%). The adverse effects listed in Table 4 were seemingly minor, but the authors did not describe the 4 “other” events in the Ketamine group. It does not appear that there were any adverse airways events and adverse airway events requiring intervention. The small sample size precludes drawing conclusions regarding rare adverse outcomes.

APPLICABILITY: The patients were pediatric patients with no mention of ethnic background or socioeconomic status. It is unclear whether difference in pain perceptions between varying ethnic groups would have produced different results for this study. The reduction in pain scores is important and balancing this benefit against potential adverse events is essential. They did not mention any significant events such as laryngospasm or requiring bag mask ventilation.

AUTHOR’S CONCLUSIONS: “In conclusion, ketamine is an effective alternative intranasal analgesic for children with moderate to severe pain from limb injury. Adverse effects were more frequent with ketamine; however, these were all relatively mild. Intranasal ketamine could be considered for children who have some contraindication to fentanyl or other opioid use. Areas for further research were identified, including assessing the effectiveness of ketamine as an analgesic in which intranasal fentanyl has failed, assessment of intranasal ketamine at the same or a lower dose or as an adjunct to fentanyl or other opioids, and exploration of the differences in pain perception and management between younger and older children.”

POTENTIAL IMPACT: Given the increase in adverse reactions in the Ketamine group, Fentanyl is likely the preferred agent via the intranasal route. However, the use of intranasal Ketamine may be considered if there is a contraindication to the use of opiates.

ANALGESIA:
INTRANASAL FENTANYL VS KETAMINE (PRIME)

In children 8-17 years of age presenting to the emergency department with an acute, painful orthopedic extremity injury is Intranasal Ketamine (1.5 mg/kg) non-inferior to Intranasal Fentanyl (1.0 mcg/kg) in reducing pain at 30 minutes from administration?

Nisha Narayanan, MD, Elizabeth Haines, MD
May 2019

Frey TM, Florin TA, Caruso M, Zhang N, Zhang Y, Mittiga MR.

EFFECT OF INTRANASAL KETAMINE VS FENTANYL ON PAIN REDUCTION FOR EXTREMITY INJURIES IN CHILDREN: THE PRIME RANDOMIZED CLINICAL TRIAL.

JAMA Pediatr. 2019 Feb 1;173(2):140-146.
PubMed ID: 30592476

STUDY DEFINITIONS	
POPULATION	Inclusion: 8-17 years, acute, orthopedic extremity injury, moderate to severe pain (visual analog pain score (VAS) > 35 mm), legal guardian present Exclusion: Significant head, chest, abdomen or spine injury GCS <15 or unable to report a VAS score Nasal trauma, aberrant nasal anatomy or active epistaxis Ketamine or Fentanyl allergy History of psychosis Opioid administration prior to arrival Non-English speaking In police custody Postmenarchal girls without a negative pregnancy test Setting: Single Children's Hospital (US), 2016-2017
INTERVENTION	Intranasal Ketamine 1.5 mg/kg (maximum dose 100 mg)
CONTROL	Intranasal Fentanyl 2.0 mcg/kg (maximum dose 100 mcg)
CO-INTERVENTION	Dose: Rounded to the nearest 0.1 ml, maximum desirable volume 2.0 ml Administered in alternating 0.5 ml aliquots between nares using an intranasal mucosal atomization device Rescue analgesic at the treating clinician's discretion
OUTCOME	Primary Outcome: Different in pain reduction at 30 minutes (ΔVAS) Secondary Outcomes: 1. Difference in pain reduction at 15 and 60 minutes (ΔVAS) 2. Sedation level: a. University of Michigan Sedation Scale (See Appendix) b. Capnography levels (hypoventilation) 3. Change in vital signs (Abnormal vital signs defined by PALS guidelines): a. Every minute for the 1st 15 minutes (via video review) b. Baseline, 15, 30 and 60 minutes 4. Adverse events (Common Terminology Criteria for Adverse Events 4th Ed) a. ED b. Post discharge (30-day Phone follow-up) 5. Rescue Medications required 6. Unscheduled return visits (30-day Phone follow-up)
DESIGN	Interventional: Randomized Clinical Trial (Non-inferiority Hypothesis)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Randomization was computer generated and in permuted blocks of 6 or 8 with 1:1 allocation within blocks (described in study protocol in supplementary materials).
Was randomization concealed?	Yes. Syringes were identical in color and individually stored in prenumbered, sealed envelopes with a weight-based dosing administration resource.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Patient were similar with regard to demographic characteristics, mechanism and type of injury, time to arrival, baseline pain scores and the requirement for reduction and sedation (Table 1).
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Clinicians were blinded to the study group. To assess blinding, study personal were asked at 30 minutes which medication was administered. Their assessment was correct 63% of the time (52% Ketamine, 74% Fentanyl). It is unclear if patients/parents and outcome assessors were blinded.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Follow up was complete for the ED study outcomes. 30 days phone follow-up was completed for 82.6% of patients (84.1% (37/44) of the Ketamine group and 81% (34/42) of the Fentanyl group)
Were patients analyzed in the groups to which they were randomized?	No. An intention to treat analysis was not completed. The primary analysis was a per protocol analysis which included 97.8% (44/45) of the patients randomized to the Ketamine group and 93.3% (42/45) of the patients randomized to the Fentanyl group. Reasons for withdrawal after randomization included: inability to provide urine for a pregnancy test, change in parental preference, clinician preference and medication unavailability.
Was the trial stopped early?	No. The trial was not stopped early. The non-inferiority margin was defined as 10 ml. Sample size determination indicated a requirement for 78 patients and 90 were enrolled to account for potential missing data.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 85 (Ketamine 43, Fentanyl 42)

PRIMARY OUTCOME: PAIN REDUCTION (TABLE2, FIGURE3)

TIME INTERVAL	KETAMINE[1]	FENTANYL[1]	FENTANYL - KETAMINE[2]
15 minutes	-24.4 (-29.3, -19.4)	-25.3 (-30.3, -20.3)	0.93 (-6.09, 7.96)
30 minutes	-30.6 (-35.8, -25.4)	-31.9 (-37.2, -26.6)	1.26 (-6.19, 8.71)
60 minutes	-27.7 (-33.8, -21.6)	-29.0 (-35.1, -22.8)	1.30 (-7.36, 9.95)

1. Mean Difference (mm) within medication group (95% CI), All significant
2. Mean Difference (mm) between medication groups (95% CI), All non-inferior
A 15 mm decrease in VAS score is considered a clinically significant improvement in pain

Secondary Outcomes
Vital Signs*: No difference in vital signs, no abnormal vital signs requiring intervention
Sedation*: No difference in highest attained score, no score > 2
Capnography: No difference in mean levels at each assessment time
Decrease in ETCO2 by ≥ 10 mm/Hg within 15 minutes: Ketamine: 20.9%, Fentanyl: 4.8%
All lasted < 30 seconds and were self-limited (i.e. did not require an intervention)
Adverse Events: 54.7% (47/86) had 63 adverse events. All minor (Grade II) and transient
Drowsiness (both), dizziness (both) and unpleased taste (K only) were the most common
Ketamine: 77% (34/44) ≥ 1AE
Fentanyl: 31% (13/42) ≥ 1AE
Relative Risk: 2.5, 95% CI (1.5, 4.0)
Rescue Medications*: Ketamine: 25% (11/44), Fentanyl: 21% (9/42), RR: 0.89, 95% CI (0.5, 1.6)
*See supplementary materials

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The upper limit for the pain score differences at 15, 30 and 60 minutes (table above) was less than the 10 ml defined by the authors for Ketamine to be considered non-inferior to Fentanyl

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. Patients are typical of those that we see with orthopedic injuries.
Were all patient important outcomes considered?	Yes. The study included relevant efficacy and safety outcomes for an analgesic study. 86% of the patients were available for 30-day phone follow-up so that post ED discharge adverse events such a sleep disturbances may be underrepresented.
Are the likely treatment benefits worth the potential harm and costs?	Intranasal Ketamine was non-inferior to intranasal Fentanyl in pain reduction at 15, 30 minutes and 60 minutes. Ketamine was associated with a higher rate of mild, transient adverse events such as drowsiness, dizziness and an unpleasant taste. There was no difference in vital signs, level or sedation or need for rescue analgesia.

CLINICAL BOTTOM LINE

BACKGROUND: Pain is typically undertreated in children. Intranasal administration of analgesics has the benefits of rapid, needleless administration and a more rapid onset compared to oral administration. Ketamine is used frequently by the intravenous or intramuscular route for procedural sedation due to its efficacy and safety. Recently sub-dissociative dosing of Ketamine as an analgesic has been studied in adults and children as an alternative to opioids.

CLINICAL QUESTION: In children 8-17 years of age presenting to the emergency department with an acute, painful, orthopedic extremity injury is Intranasal Ketamine (1.5 mg/kg) non-inferior to Intranasal Fentanyl (1.0 mcg/kg) in reducing pain at 30 minutes from administration?

DESIGN/VALIDITY: This was a well-designed randomized clinical trial at a single pediatric hospital in the US that included 85 patients in the primary, per protocol analysis. Patients were randomized to Intranasal Ketamine (1.5 mg/kg, maximum dose of 100 mg) or Intranasal Fentanyl (1.0 mcg/kg, maximum dose of 100 mcg) via a nasal atomizer device. The primary outcome was the difference between the study medications in pain score measured on a visual analog scale at 30 minutes after medication administration. Secondary outcomes included change in pain at 15 and 60 minutes, level of sedation, changes in vital signs, need for additional analgesic medication and adverse events. Randomization was computer generated and allocation was concealed. Study personnel were blinded to study group. Patient were similar with regard to demographic characteristics, mechanism and type of injury, time to arrival, baseline pain scores and the requirement for reduction and sedation (Table 1).

PRIMARY RESULTS: The primary analysis was a per protocol analysis which included 97.8% (44/45) of the patients randomized to the Ketamine group and 93.3% (42/45) of the patients randomized to the Fentanyl group. Reasons for withdrawal included: inability to provide urine for a pregnancy test, change in parental preference, clinician preference and medication unavailability.

There was a significant reduction in pain at 15, 30 and 60 minutes for both study groups. The upper limit for the pain score differences at 15, 30 and 60 minutes (table below) was less than the 10 mm defined by the authors for Ketamine to be considered non-inferior to Fentanyl.

PAIN REDUCTION (TABLE 2, FIGURE 3)

TIME INTERVAL	KETAMINE[1]	FENTANYL[1]	FENTANYL - KETAMINE[2]
15 minutes	-24.4 (-29.3, -19.4)	-25.3 (-30.3, -20.3)	0.93 (-6.09, 7.96)
30 minutes	-30.6 (-35.8, -25.4)	-31.9 (-37.2, -26.6)	1.26 (-6.19, 8.71)
60 minutes	-27.7 (-33.8, -21.6)	-29.0 (-35.1, -22.8)	1.30 (-7.36, 9.95)

1. Mean Difference (mm) within medication (95% CI), All significant
2. Mean Difference (mm) between medications (95% CI), All non-inferior

Ketamine was associated with a higher rate of having greater than or equal to one adverse event (Ketamine: 77% vs Fentanyl: 31% (Relative Risk: 2.5, 95% CI (1.5, 4.0) though adverse events were minor (Grade II) and transient. Drowsiness (both groups), dizziness (both groups) and unpleased taste (Ketamine group only) were the most common adverse events. The was no difference between the two study groups in vital signs, level of sedation or need for rescue medications.

APPLICABILITY: This was a single center study conducted in a Children's hospital emergency department. The study's results are likely generalizable to patients meeting the inclusion and exclusion criteria in similar settings.

AUTHOR'S CONCLUSION: Intranasal sub-dissociative ketamine provides effective analgesia that is not inferior to intranasal fentanyl for pain associated with acute extremity injuries in children. Ketamine was associated with more adverse events, but all were mild and transient. Ketamine should be considered for pediatric pain management in the emergency setting, especially when opioids are contraindicated or associated with increased risk, such as prior to procedural sedation.

POTENTIAL IMPACT: Intranasal, sub-dissociative dosing of Ketamine appears to be an efficacious alternative to intranasal opioids. Mild, transient adverse events (drowsiness, dizziness, unpleasant taste) were more common in the Ketamine group. A larger sample size would be necessary to determine if sub-dissociative dose Ketamine is associated with a higher rate of serious adverse events such as laryngospasm.

APPENDIX: SEDATION SCALE

UNIVERSITY OF MICHIGAN SEDATION SCALE FOR CHILDREN		
0	Awake and alert	
1	Minimally sedated	Tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated	Somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated	Deep sleep, arousable only with significant physical stimulation
4	Unarousable	

ANALGESIA:
MORPHINE DOSING (ADULTS)

In adult patients with moderate to severe acute pain in the emergency department is high dose Morphine (0.15 mg/kg) superior to standard dose Morphine (0.1 mg/kg) in terms of efficacy as measured by a change in pain score at 1 hour post administration?

Katherine Fullerton, M.D., Deborah Levine, M.D.
May 2007

Birnbaum A, Esses D, Bijur PE, Holden L, Gallagher EJ.

RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF TWO INTRAVENOUS MORPHINE DOSAGES (0.10MG/KG AND 0.15 MG/KG) IN EMERGENCY DEPARTMENT PATIENTS WITH MODERATE TO SEVERE ACUTE PAIN.

Ann Emerg Med. 2007 Apr;49(4):445-53, 453.e1-2.
PubMed ID: 16978739

STUDY DEFINITIONS	
POPULATION	Inclusion: 21- 65 years, presenting to ED, pain ≤ 7 days duration, requiring opioid analgesia as per ED attending Exclusion: Methadone use, use of opioids or Tramadol within 7 days, prior adverse reaction to Morphine, chronic pain syndrome, alcohol intoxication, pregnancy or breast feeding, systolic blood pressure < 90 mm Hg, use of monoamine oxidase inhibitors, weight > 100 kg. Setting: Single academic medical center, 3/2005-1/2006
INTERVENTION	Morphine Sulfate: 0.10 mg/kg (maximum dose 10 mg) over 4-5 minutes At 30 minutes after initial dose of Morphine: Morphine sulfate: 0.05 mg/kg (maximum dose 5 mg) over 4-5 minutes
CONTROL	Morphine Sulfate: 0.10 mg/kg (maximum dose 10 mg) over 4-5 minutes At 30 minutes after initial dose of Morphine: Placebo (identical in appearance)
OUTCOME	Primary Outcome: Pain assessment at 60 minutes (10 point verbally administered pain scale) Secondary Outcomes: 1. Pain relief at 30 and 60 minutes: None, little, moderate, a lot or complete relief 2. Satisfaction: Poor, fair, good, very good, excellent 3. Proportion Pain reduction: Pain reduction divided by initial pain score 4. Adverse events: respiratory depression, hypotension, nausea, vomiting, pruritus, need for naloxone for reversal 5. Need for rescue medication
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were distributed randomly using blocks of ten by an online random plan generator.
Was randomization concealed?	Yes. Both groups received an initial dose of Morphine 0.10 mg/kg intravenously, followed by a dose of visually identically clear liquid placebo or an additional Morphine 0.05 mg/kg intravenous. The authors state that “Allocation was concealed to prevent any influence of knowledge of treatment assignment on those enrolling patients in the study. The decision to include or exclude a participant was made and informed consent obtained without knowledge of the next assignment in the sequence.”
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Patients were similar in respect to gender, race/ethnicity, and location of pain. There was slightly more abdominal pain in the lower dose group, slightly more back pain in the higher dose group.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Patients, clinicians and research assistants were masked to group allocation. Only the pharmacy was aware of patient allocation.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Somewhat. For the primary outcome measure of pain score difference from 0 to 60 minutes, 134/138 (97%) patients in the low dose and 132/142 (93%) patients in the higher dose completed the study for all data points. The authors state that time to peak morphine analgesia is at 20 minutes, therefore pain measurements at 30 and 60 minutes should be sufficient to measure achieved analgesia.
Were patients analyzed in the groups to which they were randomized?	Yes. 138 patients were allocated to the 0.10 mg/kg group. 142 patients were allocated to the 0.15 mg/kg group. All patients were analyzed in the groups to which the were randomized (intention to treat).
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 138 patients standard dose (0.10 mg/kg) group
N = 142 patients high dose (0.15 mg/kg) group
Pain location: 2/3 abdominal/pelvic
Median Initial pain: Standard 10 (8-10), High: 9 (8-10)

Change in Pain Score at 30 minutes (after 0.1 mg/kg):
Mean Difference: 0.5, 95% CI (-0.1, 1.2)

Primary Outcome: Pain Score change 0-60 minutes
Standard Dose: 4.5 ± 3 (Mean ± SD)
High Dose: 5.3 ± 3
Mean Difference: 0.8, 95%CI (0.1, 1.5).
This was a statistically significant difference favoring the high dose group. However, this effect did not meet the a priori clinically significant change in pain score of 1.3 defined by the authors in their sample size determination

Secondary Outcomes:

Pain relief at 60 minutes
Standard Dose: 77%, 95% CI (69, 84%)
High Dose: 68%, 95% CI (59, 76%)
Risk Difference: 9%, 95% CI (-2, 20%)

Satisfaction: Good or better at 60 minutes
Standard Dose: 73%, 95% CI (64, 80%)
High Dose: 84%, 95% CI (67, 89%)
Risk Difference: 11%, 95% CI (1, 21%)

Proportional Reduction: > 50% at 60 minutes
Standard Dose: 53%, 95% CI (44, 62%)
High Dose: 67%, 95% CI (59, 75%)
Risk Difference: 14%, 95% CI (3, 26%)

Adverse Events:
No statistically significant difference between groups
The most common adverse event was nausea (12%)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See the above confidence intervals for the risk and mean differences for the primary and secondary outcomes above.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	The patients in this study were age 21-65 years. This was primary an urban Hispanic and Black population. The results cannot be directly applied to a pediatric population.
Were all patient important outcomes considered?	Yes. Change in pain score, reported pain relief, patient satisfaction and adverse events were reported.
Are the likely treatment benefits worth the potential harm and costs?	Not based on this study. Although there was no increase in adverse events, the dose of 0.15 mg/kg dose of intravenous morphine did not offer a clinically significant increase in analgesia over the traditional dose of 0.10 mg/kg.

CLINICAL BOTTOM LINE

BACKGROUND: The optimal medication and regimen to provide analgesia in the emergency department is unknown. Traditionally patients deemed to require narcotic analgesia are treated with Morphine (0.1 mg/kg). The intent of this study was to address the problem of “oligo-analgesia” in the emergency department.

CLINICAL QUESTION: In adult patients with moderate to severe acute pain in the emergency department is high dose Morphine (0.15 mg/kg) superior to standard dose Morphine (0.1 mg/kg) in terms of efficacy as measured by a change in pain score at 1 hour post administration?

DESIGN/VALIDITY: The subjects of the study were patients 21-65 years old presenting to the ED with pain of less than or equal to 7 days duration. The authors selected “low” (0.10 mg/kg) and “high” (0.15 mg/kg) dose morphine for comparison, with a primary outcome of difference in pain score between groups at 60 minutes. 280 patients were included in the primary intention to treat analysis. A potential validity concern is that although the authors purport to be comparing “low” and “high” dose morphine, they are in fact studying the differences in pain score between a single dose of 0.10 mg/kg of intravenous morphine and placebo at 30 minutes and two divided doses of morphine 0.10 mg/kg at time 0 and 0.05 mg/kg given at 30 minutes. 6% of the patients in the high dose group did not receive the second dose. This may bias the study results against the high dose group. In addition, the patient population included multiple difference source of pain though abdominal/pelvic pain was most common as is typical of patients presenting to the emergency department with pain.

PRIMARY RESULTS: There was a statistically significant greater reduction in pain score from 0-60 minutes in the high dose Morphine (0.15 mg/kg) group when compared to the standard dose (0.1 mg/kg) Morphine group. (Standard Dose: 4.5 ± 3 (Mean ± SD), High Dose: 5.3 ± 3, Mean Difference: 0.8, 95% CI (0.1, 1.5). However, this difference did not meet the a priori criteria for a clinically significant change in pain score of 1.3.

There was a statistically significant difference favoring the high dose Morphine group in the proportion of patients with “good or better” satisfaction at 60 minutes (Absolute Risk Difference: 11%, 95% CI (1, 21%) and in the proportional reduction of pain at 60 minutes (Absolute Risk Difference: 14%, 95% CI (3, 26%). There was not a statistically significant difference in adverse events or pain relief at 60 minutes.

APPLICABILITY: The study is likely generalizable to adult patients with moderate to severe acute pain meeting the study’s inclusion and exclusion criteria. It is unclear if the results in the primarily urban Black and Hispanic population would be similar in other populations.

AUTHOR’S CONCLUSION: “In conclusion, our results support the safety, but not superior analgesic effect, of an initial morphine dose of 0.15 mg/kg over the commonly used dose of 0.10 mg/kg, which has been shown to be inadequate to control acute severe pain in many patients. This finding is consistent with the hypothesis that acute pain reduction in response to increased administration of analgesics may follow a stepwise pattern in which an analgesic threshold must be reached before patients can appreciate perceptible relief. Investigation of higher analgesic doses, different analgesic agents, linear or incremental titrated dosing, or a more targeted approach to administration is warranted.”

POTENTIAL IMPACT: Though multiple studies demonstrate that pain is often inadequately controlled in the emergency department, this study did not identify a clinically significant benefit of 0.15 mg/kg of Morphine over standard dosing of 0.1 mg/kg and is unlikely to have a large impact on the way we provide analgesia to our patients.

ANALGESIA:
TOPICAL LIDOCAINE FOR ORAL ULCERS

In infants and children with poor oral intake due to infectious painful oral ulcers does topical 2% viscous Lidocaine when compared to Placebo improve oral intake within the first 1 hour after administration?

Alexis Pankow, M.D., Michael Tunik, M.D.
December 2013

Hopper SM, McCarthy M, Tancharoen C,
Lee KJ, Davidson A, Babl FE.

TOPICAL LIDOCAINE TO IMPROVE ORAL INTAKE IN CHILDREN WITH PAINFUL INFECTIOUS MOUTH ULCERS: A BLINDED, RANDOMIZED, PLACEBO-CONTROLLED TRIAL.

Ann Emerg Med. 2014 Mar;63(3):292-9.
PubMed ID: 24210368

STUDY DEFINITIONS	
POPULATION	Inclusion: 1. 6 months to 8 years 2. Clinical diagnosis of gingivostomatitis, ulcerative pharyngitis, herpangina, or hand, foot, and mouth. 3. History of poor oral fluid intake (by parent as “not drinking well” or “oral fluid intake less than 10 mL/kg of fluid in the preceding 2 hours). Exclusion: 1. Hypersensitivity to Lidocaine or other amide local anesthetics. 2. Elevated plasma levels of Lidocaine may be dangerous (epilepsy, impaired cardiac conduction, bradycardia, impaired hepatic or renal function). 3. Severely dehydrated or toxic appearing, requiring immediate resuscitation. 4. 2 episodes of vomiting before the ED presentation 5. Dental disease, mouth trauma, or malignancy; patients receiving cardiac or other drugs with possible interactions with Lidocaine. 6. ≥ 1 dose of oral topical anesthetic for the same illness. 7. Preexisting upper airway obstruction or swallowing difficulties 8. Received analgesia within 1-hour preceding enrollment. 9. Non–English speaking parents/guardians. Setting: Single Children’s Hospital ED (Australia), 11/2009-11/2012
INTERVENTION	2% Viscous Lidocaine: 0.15 ml/kg
CONTROL	Placebo: 0.15 ml/kg (identical to study drug in appearance, taste, smell)
OUTCOME	Primary Outcome: Fluid ingested within 60 minutes in milliliters/kilogram Secondary Outcomes: Short-term: 1. Whether the participant ingested more than 5, 10, or 20 ml/kg of fluid within 0 to 30 and 0 to 60 minutes. 2. Adequate oral intake at 60 minutes. 3. Additional treatment for mouth ulcers at the end of the 60-minutes Longer-term: 1. Adverse events (allergic reactions, seizures, cardiac arrhythmia, and clinical episodes of aspiration) within 90-minutes. 2. Oral hydration failures (required IV or NG fluids) within 90 minutes. 3. Required admission. 4. Length of ED stay
DESIGN	Interventional: Randomized clinical trial

ARE THE RESULTS VALID?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Randomization was with block randomization with blocks of 2 or 4.
Was randomization concealed?	Yes. Drugs were labeled as A or B and were similar in terms of taste, smell and appearance were similar. While not explicitly stated it does not appear that there was an opportunity to bias allocation into study groups
Were patients in the study groups similar with respect to known prognostic factors?	Yes. (Table 1) Oral intake slightly greater in the Placebo group in the previous 24 hours. Pre-treatment pain scores were not presented.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded	Physicians and patients were blinded. It is unlikely that lack of blinding would influence the primary outcome of oral intake at 1 hours
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Only 1 patient withdrew from the study before the end of observation period
Were patients analyzed in the groups to which they were randomized?	Yes. Both an intention to treat and a per protocol analysis were completed. No patients switched groups or broke protocol. 2 patients received Acetaminophen during the trial period in the Lidocaine group
Was the trial stopped early	No. The study was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Primary Outcome: Median Fluid Intake
Lidocaine: 8.49 ml/kg IQR (4.07, 13.84)
Placebo: 9.31 ml/kg IQR (3.06, 15.18)
Median Difference (Placebo - Lidocaine) = 0.82 ml/kg, 95%CI (-2.52, 3.60 ml)

Primary Outcome: Mean Fluid Intake
Lidocaine: 9.48 ml/kg standard deviation 7.02
Placebo: 9.32 ml/kg standard deviation 7.39
Mean Difference (Placebo – Lidocaine) = 0.15 ml/kg 95%CI (-2.7, 3.0 ml)

There was no statistical difference between median or mean fluid intake within the first hour after study drug administration. The differences found were less than the clinically significant difference of 4.0 ml/kg that the authors specified in their sample size determination.

Secondary Outcomes: No difference in:
Received additional analgesia
Need for intravenous or naogastric hydration

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See the confidence intervals for the mean and median differences above.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Yes. Patients have the same disease processes in our patient population. It is unclear if pain or tolerance of oral ulcers differ would differ in a more diverse patient population.
Were all clinically important outcomes considered?	No. Pre and post pain scales, parental satisfaction, and parental comfort with ability of the child to drink after discharge were not assessed
Are the likely treatment benefits worth the potential harm and costs?	No benefit or adverse effects were identified.

CLINICAL BOTTOM LINE

BACKGROUND: Painful oral mouth ulcers can limit oral intake and lead to dehydration. Topical agents such as Benadryl, Maalox and viscous Lidocaine are sometimes used to reduce pain though no randomized clinical trials of these agents have been completed in otherwise healthy children.

CLINICAL QUESTION: In infants and children with poor oral intake due to infectious painful oral mouth ulcers does topical 2% viscous Lidocaine when compared to Placebo improve oral intake within the first 1 hour after administration?

DESIGN/VALIDITY: This study is a blinded, placebo controlled randomized clinical trial of topical Lidocaine for painful, infectious oral lesions in 100 children (50 in each group) in a single emergency department in Australia. This was a well-designed study with few validity concerns. Patients represented a convenience sample and fluid intake was used as a surrogate measure of improvement in pain rather than a change in pain score. Parental satisfaction was not assessed.

PRIMARY RESULTS: There was no clinically of statistically significant difference in mean or median fluid intake within an hour of study drug administration. The differences found were less than the authors clinically significant difference of 4.0 ml/kg

	LIDOCAINE	PLACEBO	DIFFERENCE
Median Intake (IQR)	8.49 ml/kg	9.31 ml/kg	0.82 ml/kg 95%CI (-2.52, 3.60)
Mean Intake (SD)	9.48 ml/kg	9.32 ml/kg	0.15 ml/kg 95%CI (-2.7, 3.0)

There was no difference in the secondary outcomes of received additional analgesia in the study period or need for intravenous or nasogastric hydration.

APPLICABILITY: It is unclear if these results in an Australian emergency department setting would be applicable (generalizable) to other populations or settings though there is no specific reason to think that it would not.

AUTHOR'S CONCLUSION: "In conclusion, this study found that viscous Lidocaine is not superior to a flavored gel placebo in improving oral intake in otherwise healthy children with painful infectious mouth ulcers. It appears that staff coaching and possibly the coating effect of oral topical agents alone can increase oral intake."

POTENTIAL IMPACT: Though viscous Lidocaine if sometimes used in these patients, this study did not identify a benefit to its use compared to placebo so the potential risk of an adverse event outweighs any benefit. Education about oral administration of fluids may be just as worthwhile as topical medications. Oral analgesics such as acetaminophen or ibuprofen may be more useful than topical medications and are more familiar to parents for continued therapy at home though this would require further study.

PROCEDURAL SEDATION
ADVERSE EVENT RISK FACTORS

In patients, less than 18 years undergoing parenteral procedural sedation in the ED, does the medication regimen, procedure type, pre-procedural medications, fasting status, current or underlying health risks, and demographic characteristics (age, sex, BMI) increase the risk of serious adverse events, significant interventions performed in response to an adverse event, oxygen desaturation and/or vomiting?

Nisha Narayanan, MD, Michael Mojica, MD.
December 2017

Bhatt M, Johnson DW, Chan J, Taljaard M, Barrowman N, Farion KJ, Ali S, Beno S, Dixon A, McTimoney CM, Dubrovsky AS, Sourial N, Roback MG; Sedation Safety Study Group of Pediatric Emergency Research Canada (PERC).

RISK FACTORS FOR ADVERSE EVENTS IN EMERGENCY DEPARTMENT PROCEDURAL SEDATION FOR CHILDREN.

JAMA Pediatr. 2017;171(10):957–964.
PubMed ID: 28828486

STUDY DEFINITIONS	
POPULATION	Inclusion**:** Children <18 who received sedation for a painful ED procedure by an ED physician Exclusion**:** Received medication purely for anxiolysis or analgesia without intent of sedation. if there was a language barrier, Setting: 6 Canadian Pediatric EDs, 7/2010- 2/2015
EXPOSURE	1. Sedation medication regimen 2. Demographic characteristics: Age, sex, BMI, ASA Classification 3. Pre-procedure medications: Opioids, antiemetics 4. Fasting status: Solids (4 and 6 hours) and liquids (2 hours) 5. Current respiratory illness 6. Underlying health risk 7. Procedure type
NO EXPOSURE	1. Ketamine alone 2-6. Absence of patient characteristics, pre-procedural interventions 6. Orthopedic reductions alone
OUTCOME	Primary Outcomes 1. Serious Adverse Events: Apnea, laryngospasm, hypotension, bradycardia, complete airway obstruction, clinically apparent pulmonary aspiration, permanent neurologic injury and death. 2. Significant Interventions: Performed in response to an adverse event. Positive pressure ventilation, endotracheal intubation, administration of vasoactive medications or neuromuscular blockade, chest compressions. 3. Oxygen Desaturation: Desaturation and ≥ 1: Tactile stimulation, airway repositioning, oxygen administration or increased oxygen, positive pressure ventilation 4. Vomiting: Expulsion of gastric contents through mouth or nose during sedation induction, maintenance or ED recovery phases. Secondary Outcomes: 1. Sedation Medication Dose: Total dose per kg of body weight. 2. Duration of Sedation: Time from first sedation medication administration to physiologic recovery. 3. ED Length of Stay: Time from first sedation medication to ED discharge. 4. Successful Sedation: a. Procedure completed and patient did not have unpleasant recall of the procedure, did not resist or require active restraint during the procedure and did not experience a permanent complication from the sedation b. Procedure not abandoned because of a sedation-level adverse event
DESIGN	Observational: Prospective cohort study

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	Unclear. There was no table comparing all characteristics of Ketamine alone (largest patient subgroup) or orthopedic reductions vs non-orthopedic reductions but some comparisons are available in the supplement to the article. Logistic regression was used to determine the independent association of each potential risk factor while accounting for the effects of potential confounders.
Were the circumstances and methods for detecting the outcome similar?	Yes. Documentation of study data, training to complete data collection and study definitions were standardized.
Was follow-up sufficiently complete?	Yes. Follow-up was sufficiently complete because outcomes did not extend past ED discharge and all patients were followed to ED discharge. There was no assessment of post sedation adverse events after discharge such as vomiting or sleep disturbance.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

DEMOGRAPHIC CHARACTERISTICS	
Population	N = 6,295, 66% male, mean age 8.0 ± 4.6 years
Procedure Success	95% success, 4% with active resistance, 1% procedures not completed
Sedation Regimen	Ketamine 62.2%, Ketamine/Propofol 13.5%, Propofol/Fentanyl 11.5%
Procedures	Orthopedic Reduction 65.6%, laceration repair 16.3%
Pre-procedure	Opioid 28.8%
Pre-procedure	Antiemetic (with Ketamine): 93.3%
ASA Class I or II	97.7%
Fasting Duration	Solids ≤ 6 hours: 48.1%, Solid ≤ 4 hours: 16.2%, Liquid ≤ 2 hours: 5.0%
Underlying Health Risk	3.2%
Respiratory Illness	8.2%

INCIDENCE OF SEDATION RELATED ADVERSE EVENTS	
Adverse Events	11.7%, 95% CI (6.4, 16.9%), 831 events in 736 patients Oxygen desaturation, vomiting most common
Serious Adverse Events	1.1%, 95% CI (0.5, 1.7%). Apnea (0.9%), laryngospasm (0.1%), hypotension (0.1%), bradycardia (0.1%) No complete airway obstruction, pulmonary aspiration, permanent neurologic disability or death occured
Significant Interventions	1.4%, 95% CI (0.7, 2.1%) 86 patients, All (+) pressure ventilation
Oxygen desaturation	5.6%, 95% CI (2.0, 9.2%)
Vomiting	5.2%, 95% CI (2.4, 8.0%)

SEDATION TIME INTERVALS		
	Sedation Duration Median (IQR)	ED Length of Stay Median (IQR)
Propofol alone (shortest)	51 (45, 126) minutes	67 (43, 196) minutes
Ketamine + Fentanyl (longest)	177 (84, 145) minutes	132 (100, 164) minutes

FACTORS SIGNIFICANTLY ASSOCIATED WITH ADVERSE EVENTS		
ADVERSE EVENT	RISK FACTOR	ODDS RATIO* (95% CI)
Serious Adverse Events	Ketamine + Fentanyl	6.48 (2.52, 15.22)
	Ketamine + Midazolam	3.60 (1.10, 9.45)
	Ketamine + Propofol	4.42 (2.25, 8.74)
	Propofol + Fentanyl	3.15 (1.46, 6.74)
	Propofol only	5.59 (2.26, 13.08)
Significant Interventions	Ketamine + Fentanyl	3.97 (1.77, 8.14)
	Ketamine + Propofol	2.18 (1.24, 3.70)
	Pre-procedure Opioid	2.18 (1.36, 5.52)
	Laceration repair	2.39 (1.13, 5.75)
Oxygen Desaturation	Ketamine + Fentanyl	2.46 (1.54, 3.80)
	Ketamine + Propofol	2.22, (1.64, 2.99)
	Age in 5 year increments	1.26 (1.09, 1.46)
	Pre-procedure Opioid	2.07 (1.62, 2.65)
	Laceration repair	1.61 (1.11, 2.30)
	Lumbar puncture	2.83 (1.44, 5.13)
	Other procedures	2.06 (1.35, 3.07)
	Pre-oxygenation	0.39 (0.25, 0.60)
Vomiting	Ketamine + Fentanyl	1.87 (1.21, 2.82)
	Ketamine + Propofol	0.25 (0.15, 0.39)
	Other medication	0.15 (0.02, 0.53)
	Propofol + Fentanyl	0.02 (0.002, 0.05)
	Propofol	0.01 (0.001, 0.09)
	Pre-procedure Opioid	1.47 (1.13, 1.90)
	Pre-procedure Antiemetic	0.52 (0.40, 0.69)
	Laceration Repair	1.70 (1.18, 2.42)

GREEN = Risk factor associated with a decreased risk of the specified adverse event
*Medication Regimen odds ratio denominator is Ketamine only regimen
*Procedure Type odds ratio denominator is Orthopedic reduction

HOW PRECISE IS THE ESTIMATE OF THE RISK?
Estimated odds ratios with 95% profile likelihood CIs were reported. See table above for factors with a significant association. The study had a large sample size so narrow confidence intervals are expected. However, for infrequent risk factors larger confidence intervals are expected.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Yes. The study was performed in tertiary academic children's hospitals undergoing similar procedures.
Was follow-up sufficiently long?	Yes. Follow-up was sufficiently complete because outcomes did not extend past ED discharge and all patients were followed to ED discharge. There was no assessment of post sedation adverse events after discharge such as vomiting or sleep disturbance.
Is the exposure similar to what might occur in my patient?	Yes. Demographic characteristics, fasting status, current and underlying health risk are similar. There were similar indications for sedation as well. The Ketamine combination regimens and pre-Ketamine antiemetics are not utilized frequently in our institutions.
What is the magnitude of the risk?	The odds ratios for significant predictors are presented above. The largest odds ratio for serious adverse events were for Ketamine + Fentanyl (6.48 (2.52, 15.22)) and Propofol only (5.59, (2.26, 13.08)) when compared to Ketamine only. The largest odds ratio for significant intervention was for Ketamine + Fentanyl 5.59, (2.26, 13.08) when compared to Ketamine only. Propofol only (0.01 (0.001, 0.09)) and Propofol + Fentanyl 0.02 (0.002, 0.05) were associated with the greatest reduction in vomiting compared to Ketamine alone. Absolute risk or odds were not presented to determine the incremental risk.
Are there any benefits that offset the risks associated with exposure?	Yes. Sedation is often necessary to complete a painful procedure. The study identified some factors that are associated with both an increased or decreased risk of serious adverse events. Many of these factors can be altered to result in a decreased risk of sedation adverse events such as not using Ketamine in combination with other sedation medications and using a pre-procedure antiemetic is Ketamine is to be used.

CLINICAL BOTTOM LINE

BACKGROUND: Procedural sedation for children undergoing painful procedures is standard in the Emergency Department. There is a need to identify risk factors for serious adverse events but previous studies are limited by single-center design and/or are underpowered to identify such factors as many of the adverse events occur infrequently.

CLINICAL QUESTION: In patients, less than 18 years undergoing parenteral procedural sedation in the ED, does the medication regimen, procedure type, pre-procedural medications, fasting status, current or underlying health risks, and demographic characteristics (age, sex, BMI) increase the risk of serious adverse events, significant interventions performed in response to an adverse event, oxygen desaturation, and/or vomiting?

DESIGN/RISK OF BIAS: The was a prospective cohort study the included 6, 295 children in 6 children's hospital Emergency Department in Canada over 4.5 years. The study utilized standardized outcome definitions, novel documentation processes that helped ensure data integrity, and included kids from a variety of practice settings who were sedated with 6 different medication regiments for a range of painful procedures. This was an observational study design so that direct causal conclusions cannot be drawn from the associations demonstrated. No cases of sedation-related pulmonary aspiration, neurologic injury, or death during the study period at any of study sites so conclusions regarding these adverse events cannot be made.

PRIMARY RESULTS: The patients were primarily well (97% ASA class I or II, 3.2% with an underlying health risk. Ketamine alone (62.2%) was the primary sedation regimen utilized but other regimens accounted for a significant proportion of sedations (Ketamine/Propofol 13.5%, Propofol/Fentanyl 11.5%). Orthopedic reduction (65.6%) was the most common procedure performed. The procedure was successfully completed 95% of the time with an addition 4% completed but with active resistance by the patient.

Sedation-related adverse events occurred in 1 in 10 patients (11.7%, 95% CI (6.4, 16.9%)), but only 1 in 100 patients (1.1%, 95% CI (0.5, 1.7%)) had a serious adverse event. Oxygen desaturation (5.6%, 95% CI (2.0, 9.2%)) and vomiting (5.2%, 95% CI (2.4, 8.0%)) were the most common sedation related adverse events. Apnea (0.9%) was the most common serious adverse event. Laryngospasm (0.1%), hypotension and (0.1%), bradycardia (0.1%) occurred less frequently
There was no complete airway obstruction, pulmonary aspiration, permanent neurologic disability or death. Positive pressure ventilation was the only significant intervention required (1.4%, 95% CI (0.7, 2.1%).

Risk factors associated with an increased risk of serious adverse events included the use of Ketamine in combination with other medications or non-Ketamine regimens when compared to Ketamine alone. There was no significant difference in the type of procedure associated with serious adverse events.

Risk factors associated with an increased risk for significant interventions included combination Ketamine sedation, laceration repair, and pre-procedural opioids. The time from the administration of pre-procedure opioid to initiation of sedation was not presented. Since, analgesia should be provided in patients with significant pain, it would have been helpful to know if a longer interval between medications would reduce risk.

Risk factors associated with an increased risk of oxygen desaturations included combination Ketamine sedation, pre-procedural opioids, lumbar punctures, and laceration repairs. Pre-oxygenation was associated with a decreased risk of desaturations.

Risk factors associated with an increased risk of vomiting included the use of Ketamine alone and in combination with another medication and the use of pre-procedural opioids. Pre-procedure anti-emetics decreased the risk of vomiting after sedation.

Ketamine dose was not associated with serious adverse events but higher doses were associated with higher rates of oxygen desaturation and vomiting. It is unclear if the dosing provided was the initial dose or if additional dosing was required.

APPLICABILITY: The inclusion of a large sample size, a variety of sedation regimens and procedures performed likely make the study's results generalizable to the children's hospital emergency department setting. The generalizability of results to practice in general or community hospitals or non-Emergency department settings is unclear.

AUTHOR'S CONCLUSIONS: "The large, multicenter cohort in this study shows that ED procedural sedation for children in this setting is safe, with a low overall incidence of SAEs and interventions. Sedation with Ketamine alone was associated with the best outcomes, with significantly fewer SAEs and interventions than Ketamine combined with either propofol or fentanyl."

POTENTIAL IMPACT: The incidence of adverse events (1 in 10), serious adverse events (1 in 100) and interventions (1 in 70) emphasize the need for close monitoring and the presence of dedicated sedation personnel with pediatric airway skills.

The use of non-ketamine sedative or Ketamine in combination with other sedative should be undertaken with caution. Practitioners may consider giving Zofran or another anti-emetic prior to sedation with Ketamine. We must be careful about pre-procedural opioids, understanding that they may increase the risk of serious adverse events, oxygen desaturation, and vomiting prior to ED discharge though withholding analgesia in patients with significant pain would be unethical. The provision of supplemental oxygenation may be beneficial prior to sedations in reducing desaturations.

PROCEDURAL SEDATION: KETAMINE ADVERSE EVENTS

In children receiving Ketamine for procedural sedation in the emergency department are there patient and procedural factors that are predictive of airway and respiratory adverse events?

Vaishali Shah, M.D., Jessica Foltin, M.D.
March 2009

Green SM, Roback MG, Krauss B, Brown L, McGlone RG, Agrawal D, McKee M, Weiss M, Pitetti RD, Hostetler MA, Wathen JE, Treston G, Garcia Pena BM, Gerber AC, Losek JD; Emergency Department Ketamine Meta-Analysis Study Group.

PREDICTORS OF AIRWAY AND RESPIRATORY ADVERSE EVENTS WITH KETAMINE SEDATION IN THE EMERGENCY DEPARTMENT: AN INDIVIDUAL-PATIENT DATA META-ANALYSIS OF 8,282 CHILDREN.

Ann Emerg Med. 2009 Aug;54(2):171-80. e1-4.
PubMed ID: 9501426

STUDY DEFINITIONS	
POPULATION	Inclusion: Children (≤ 21 years), parental Ketamine administration for emergency department procedural sedation. Exclusion: Abstracts, case reports, case-control studies, case series of < 20 subjects, did not include drug doses, adverse effects, Propofol co-administered. Setting: 32 ED's, Included studies: 1997-2008
INTERVENTION	Candidate Predictors: Selected based on prior literature and biologic plausibility Medication variables: 1. Route: Intravenous or intramuscular 2. Intravenous dose: High: Initial ≥ 2.5 mg/kg, total ≥ 5 mg/kg 3. Intramuscular dose: Low < 3 mg/kg 4. Co-administration of an anticholinergic (yes/no) 5. Co-administration of a benzodiazepine (yes/no) Patient variables: 1. ASA physical status (1-2 and ≥ 3) 2. Age: < 2 years, 2-12 years, ≥ 13 years 3. Oropharyngeal procedure (yes/no)
CONTROL	Absence of the predictor or reference class of predictor. e.g. age 2-12 years
OUTCOME	Primary Outcome: Airway and respiratory adverse events 1. Upper airway obstruction: Stridor, hypoventilation, oxygen desaturation that resolved with repositioning of the airway 2. Apnea: Cessation of spontaneous respirations considered significant by observers, decrease in oxygen saturation to 90% 3. Laryngospasm: Stridor or other evidence of airway obstruction that did not improve with airway alignment maneuvers Secondary Outcomes: Specific occurrence of apnea, laryngospasm (described above)
DESIGN	Systematic Review and Meta-analysis of Cohort studies

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review explicitly address a sensible clinical question?	Yes. The primary outcome was airway or respiratory adverse events which included: airway obstruction, apnea and laryngospasm. The secondary goal was analysis of laryngospasm and apnea independently. It is not clear why airway obstruction was not assessed independently as well.
Was the search for relevant studies detailed and exhaustive?	Yes. Medline searched 1966-2008. Did not include other databases such as EMbase. Authors were contacted to determine other reports that were missing from the listing. No analysis of potential publication bias was reported.
Was the risk of bias of the primary studies assessed?	Unclear. No standardized method was used to evaluate study quality. A sensitivity analysis was completed to determine if prospective studies results compared to both prospective and retrospective results collectively.
Were the selection and assessment of studies reproducible?	Unclear. No inter-rater reliability was reported. It does not appear that multiple authors assessed studies for inclusion/ exclusion criteria or study quality.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

Table 1. Study adverse event rates differed greatly. No analysis of heterogeneity was reported.

WHAT ARE THE OVERALL RESULTS OF THE REVIEW?

N = 32 studies, 8,282 patients

Patient/Procedure Characteristics
ASA 1-2: 93%
Oropharyngeal procedure: 3.2%
Intravenous: 69%
Anticholinergic: 65%
Benzodiazepine: 33%

Adverse Event Rates
Total Airway/Respiratory adverse effects: n = 329 (3.9%)
Laryngospasm: n = 22 (0.3%)
Apnea: n = 63 (0.8%)
Other: n = 234 (2.8%)
Intubated or received paralytics: N = 0 (0% CI 0.0, 0.04%)

Regression Analysis (Tables 3,4 and 5)
aOR = Adjusted Odds Ratio
* = Statistically significant

Age < 2 years/2-12 years
Airway/Respiratory: aOR 2.00, 95% CI (1.47, 2.72)*
Apnea: aOR 1.63, 95% CI (0.81, 3.30)
Laryngospasm: aOR 1.41, 95% (0.47, 4.26)

Age ≥ 13 years/2-12 years
Airway/Respiratory: aOR 2.72, 95% CI (1.97, 3.75)*
Apnea: aOR 2.86, 95% CI (1.43, 5.73)*
Laryngospasm: aOR 1.41, 95% CI (0.47, 4.26)

High IV Dosing/Not High IV Dose
(High = Initial dose ≥ 2.5 mg/kg, total dose ≥ 5.0 mg/kg)
Airway/Respiratory: aOR 2.18, 95% CI (1.59, 2.99)*
Apnea: aOR 5.11, 95% CI (2.85, 9.16)*
Laryngospasm: aOR 2.15 (0.78, 5.86)

Low IM dose (< 3 mg/kg)/Not Low IM Dose
Airway/Respiratory: aOR 0.35, 95% CI (0.16, 0.76)*
Apnea: Zero events
Laryngospasm: Zero events

Anticholinergics Co-administered (Y/N)
Airway/Respiratory: aOR 1.82, 95% CI (1.36, 2.42)*
Apnea aOR 2.06, 95% CI (1.1, 3.84)*
Laryngospasm: Not assessed

<u>Benzodiazepine Co-administered (Y/N)</u> Airway/Respiratory: aOR 1.39 (1.08-1.78)* Apnea: aOR 1.71, 95% CI (0.95, 3.05) Laryngospasm: Not assessed <u>Oropharyngeal Procedures (Y/N)</u> Airway/Respiratory: aOR 2.01, 95% CI (1.29, 3.12)* Apnea: aOR 2.41, 95 CI (1.06, 5.46)* Laryngospasm: aOR 3.75, 95% CI (1.07, 13.07)* ASA class (1-2, ≥ 3) and dosing route (IV/IM) were not independent predictors of adverse events, apnea, or laryngospasm.
DID THE REVIEW ADDRESS CONFIDENCE IN EFFECT ESTIMATES
See 95% confidence intervals for the odds ratios presented above.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were all patient-important outcomes considered?	No. Additional outcomes of interest include: length of procedure, use of supplemental oxygen, use of opioids, effect of benzodiazepines on emesis and emergence reactions and sedation efficacy. Analysis of airway obstruction separately from the composite outcome of airway/respiratory adverse events also would have been helpful.
Are any postulated subgroup effects credible?	A sensitivity analysis including only prospective studies 75% (24/32) was included. Differences in statistical significance from the analysis of all patients included: Oropharyngeal procedures were no longer predictive of respiratory/airway events, apnea of laryngospasm. High dose intravenous Ketamine was no longer a predictor of laryngospasm. Anticholinergics <u>were not</u> and benzodiazepines <u>were</u> a predictor of apnea.
What is the overall quality of the evidence?	The meta-analysis was conducted in accordance with the QUality Of Reporting Of Meta-analysis (QUOROM) guidelines. An assessment of study quality was not presented.
Are the benefits worth the costs and potential risks?	Not applicable. This was not an efficacy study so a risk benefit analysis is not possible. Adverse events were rare and managed non-invasively.

CLINICAL BOTTOM LINE

BACKGROUND: Ketamine has many properties that make it a safe and effective for procedural sedation in pediatric patients. However, rare adverse airway events such as airway obstruction, apnea and laryngospasm may occur. The ability to risk stratify for adverse events based on patient and procedural factors could potentially reduce the risk of adverse events.

CLINICAL QUESTION: In children receiving Ketamine for procedural sedation in the emergency department are there patient and procedural factors that are predictive of airway and respiratory adverse events?

DESIGN/RISK OF BIAS: This is a well-designed meta-analysis of studies of children receiving Ketamine for sedation in the emergency department. 32 emergency department based studies including 8,282 patients were included. 75% (24/32) of studies were prospective. The primary outcome of airway and respiratory adverse events was a composite outcome that included: airway obstruction and/or apnea and/or laryngospasm. Laryngospasm and apnea were also analyzed as independent outcomes. It is not clear why airway obstruction was not assessed independently. The authors analyzed the data as both a total cohort and a prospective study only cohort to assess the impact of the greater potential for bias inherent of retrospective studies. Potential biases due to a retrospective design and the limitation of observational data should be considered. Variables, other than those assessed, such as concomitant opiate use or variation in the dosing of anticholinergics and benzodiazepines were not assessed.

PRIMARY RESULTS: 3.9% of patients had an airway or respiratory adverse events (apnea 0.8%, laryngospasm 0.3%). Variation in the rate of adverse events from study to study (Table 1) could have resulted from random variation or differences in physician or institutional practice style or variation in definitions of adverse events.

The study's primary analysis including all patients identified an increase odds (aOR: 2.18, 95% CI (1.59, 2.99)) of airway and respiratory adverse events with high initial intravenous dosing (≥ 2.5 mg/kg), or high total intravenous dosing of Ketamine (> 5.0 mg/kg). The extremes of age were also identified as predictors. Those less than 2 years (aOR 2.00, 95% CI (1.47, 2.72)) and those greater than 13 years (aOR 2.27, 95% CI (1.97, 3.75) had more airway and respiratory adverse events. The co-administration of and anticholinergic (aOR 1.82, 95% CI (1.36, 2.42)) or a benzodiazepine (aOR 1.39, 95% CI (1.08, 1.78) was associated with an increased odds of adverse events and apnea. Factors associated with apnea and laryngospasm analyzed independently are presented in the table belowAmerican society of anesthesiologist classification (≥ 3) and route of administration (intravenous or intramuscular) were not significant independent predictors of airway and respiratory adverse events, apnea or laryngospasm. An oropharyngeal procedure (aOR 2.01, 95% CI (1.29, 3.12)) was associated with an increased risk of airway or respiratory adverse events, as well as apnea and laryngospasm though this was not the case when only prospective studies (aOR 1.30, 95% CI (0.77, 2,18) were included in the analysis.

TOTAL SAMPLE	AIRWAY, RESPIRATORY[1] (N = 329 (3.9%))	APNEA (N = 63 (0.8%))	LARYNGOSPASM[2] (N = 22 (0.3%))
aOR (numerator/denominator)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
< 2 years/2-12 years	2.00 (1.47, 2.72)	1.63 (0.81, 3.30)	1.41 (0.47, 4.26)
≥ 13 years/2-12 years	2.27 (1.97, 3.75)	2.86 (1.43, 5.73)	Zero Events
ASA ≥ 3 (Y/N)	1.48 (0.58, 3.72)	Zero Events	Not Assessed
High IV dose/Not High IV dose	2.18 (1.59, 2.99)	5.11 (2.85, 9.16)**	2.15 (0.78, 5.86)*
Low IM dose/Not low IM dose	0.35 (0.16, 0.76)	Zero Events	Zero Events
Intravenous/Intramuscular	1.38 (0.99, 1.90)	2.26 (0.85, 5.99)	Not Assessed
Oropharyngeal procedure (Y/N)	2.01 (1.29, 3.12)**	2.41 (1.06, 5.46)**	3.75 (1.07, 13.07)**
Anticholinergic (Y/N)	1.82 (1.36, 2.42)	2.06 (1.1, 3.84)**	Not Assessed
Benzodiazepine (Y/N)	1.39 (1.08, 1.78)	1.71 (0.95, 3.05)*	Not Assessed

1 = Airway obstruction and/or apnea and/or laryngospasm
2 = Laryngospasm: Total number of outcomes insufficient. Only the 3 variables with the highest biologic plausibility analyzed (Age<2 years, high dose IV Ketamine, oropharyngeal procedure)
GREEN = statistically significant adjusted odds ratio from regression analysis
* = was not a statistically significant predictor in the analysis of only prospective studies
** = was a statistically significant predictor in the analysis of only prospective studies

APPLICABILITY: The large number of studies (n=32) and patients (8,535) included make the study's results likely generalizable to the majority of pediatric patients receiving procedural sedation with Ketamine in the emergency department setting. However, 3 of the 32 included studies accounted for 44% of the study patients.

AUTHOR'S CONCLUSION: "In summary, risk factors for ketamine-associated airway and respiratory adverse events are high intravenous doses, administration to children younger than 2 years or aged 13 years or older, and the use of co-administered anticholinergics or benzodiazepines. Such risk is not independently altered by route (intravenous versus intramuscular), oropharyngeal procedures, or underlying physical illness. This information can be used to help risk-stratify children before Emergency Department sedation and guide ketamine administration technique. Our data do not support the regular or routine use of anticholinergics or benzodiazepines, although the effect of these agents on emesis and unpleasant recovery reactions was not studied."

POTENTIAL IMPACT: The overall rate of 3.9% airway or respiratory adverse events highlights the importance of the presence of caregivers with training and expertise in pediatric airway management. The factors identified are independent predictors of adverse airway and respiratory events: extremes of age, high intravenous or total dose or Ketamine or the co-administration of an anticholinergic or benzodiazepine can be used to modify patient selection or the approach to administration. The use of anticholinergics and benzodiazepines was not supported by the study though potential benefits of these agents was not assessed.

PROCEDURAL SEDATION: KETAMINE ROUTE

In children undergoing procedural sedation for fracture reduction in the emergency department does the route of administration of Ketamine (intravenous versus intramuscular) influence the efficacy, length of sedation and rate of adverse events?

Rachel Kowalsky, M.D., Michael Mojica, M.D.
November 2006

Roback MG, Wathen JE, MacKenzie T, Bajaj L.

A RANDOMIZED, CONTROLLED TRIAL OF INTRAVENOUS VERSUS INTRAMUSCULAR KETAMINE FOR SEDATION OF PEDIATRIC PATIENTS RECEIVING EMERGENCY DEPARTMENT ORTHOPEDIC PROCEDURES.

Ann Emerg Med. 2006 Nov;48(5):605-12.
PubMed ID: 17052563

STUDY DEFINITIONS	
POPULATION	Inclusion: 4 months-18 years, orthopedic injury requiring procedural sedation for reduction. American Society of Anesthesiologists grade I or II Exclusion: Contraindications to Ketamine: Hypertension, glaucoma, acute globe injury, increased intracranial pressure, central nervous system mass lesion, major psychiatric disorder, porphyria, previous adverse reaction to Ketamine Setting: Single Children's Hospital ED, 7/2000-10/2004
INTERVENTION	Ketamine: 1 mg/kg Intravenously (maximum dose 100 mg) over 1-2 minutes
CONTROL	Ketamine: 4 mg/kg Intramuscularly (maximum dose 200 mg)
CO INTERVENTION	Glycopyrrolate 5 mcg/kg (maximum dose 250 mcg) by same route as study medication. Subsequent doses of Ketamine at attending physician discretion
OUTCOME	Primary Outcomes: Video-taped from informed consent until ready for discharge 1. Adverse Events: Vomiting (video review), Respiratory: apnea (use of bag-valve mask), laryngospasm (audio), oxygen desaturations < 90% (use of supplemental oxygen) Behavioral distress score: pre, during IV/IM, during reduction, after sedation 2. Efficacy of Sedation: Orthopedist, parental satisfaction, pain experienced pre-sedation, during IV placement or IM injection and during reduction 3. Length of Sedation: Ketamine administration until discharge criteria met
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. A random allocation sequence was determined from a computer-generated, random-number table.
Was randomization concealed?	Likely yes. Following randomization, allocation was performed by a nurse who had access to the randomization table and placed the patient's name in the next open slot on the table. The article does not explicitly state that randomization was concealed.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Though there were some minor differences. For example, the intravenous group had more males and more African American patients. The difference with the most potential significance is the percent of patients receiving multiple doses of medication (25% in the intravenous group versus 9% in the intramuscular group). If intravenous patients received a higher than equivalent dose of Ketamine it may bias the study results toward more adverse events with intravenous Ketamine and improved or prolonged sedation.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Nurse, physicians and patients were aware of group allocation. Lack of blinding is a concern here, especially for subjective outcomes measures such as pain and satisfaction scores.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Follow up was complete for all outcomes except for emesis and respiratory events at home. This information was available for 76% of the intravenous group and 74% of the intramuscular group. Videotapes were available for 190/208 (91.3%).
Were patients analyzed in the groups to which they were randomized?	Yes. 5 patients allocated to the intramuscular group ultimately received intravenous Ketamine. However, analysis was performed on an intention-to-treat basis.
Was the trial stopped early?	Yes. The sample size determining required 282 patients. 208 were enrolled. Terminated early at nursing request because differences in duration of recovery and emesis hindered enrollment.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

RESPIRATORY EVENTS			
	INTRAVENOUS	INTRAMUSCULAR	RISK DIFFERENCE (95% CI)
Events	11% (12/109)	4% (4/99)	7% (0.5, 14.6%)
Intervention	16.5% (18/109)	7% (7/99)	9.4% (0.5, 18.3%)

The authors considered a 10% difference to be clinically significant in their sample size determination

Desaturations:
Risk Difference: IV (8.3%) – IM (4.0%) = 4.2%, 95% CI (-2.8, 11.3%)

Vomiting in the ED
Risk Difference: IM (26.2%) – IV (11.9%) = 14.3%, 95% CI (3.7, 24.9%)

Pain during procedure: (FACES scale): IV > IM sig

Distress
During procedure: IV > IM
Other times: No difference: Pre-sedation, IV/IM placement, or post-sedation

Sedation Efficacy:
Parental satisfaction: No difference in ED or 3 days
Physician satisfaction: No difference, NS

Length of Sedation:
Significantly longer in the IM group
Median IM (129 minutes) vs IV (80 minutes)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See 95% confidence intervals, above.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Probably. However, the article does not specify which orthopedic procedures were being done.
Were all patient important outcomes considered?	One important outcome that might have been included is the number of attempts needed to successfully reduce the injury. Interestingly, while they presented the need for additional dosages in Table 1 they did not include this as an efficacy measure though this may not be entirely related to sedation depth
Are the likely treatment benefits worth the potential harm and costs?	Probably. In terms of efficacy, the IM group demonstrated significantly less pain during the procedure and required additional dosages less often. In terms of safety, there were less respiratory adverse events in the IM group. Though the difference was statistically significant it did not reach the 10% that the authors required for clinical significance. No adverse effect in the IM group required subsequent IV placement. However, there was more emesis and increased length of sedation in the IM group. The increased emesis did not measurably alter levels of parent satisfaction. The number needed to treat is 1/ARD = 1/0.07 = 14 for any adverse respiratory event. 14 patients would need to be treated with IM compared to IV Ketamine to prevent 1 additional adverse respiratory event.

CLINICAL BOTTOM LINE

BACKGROUND: Intramuscular (IM) and intravenous (IV) Ketamine has been well established to be safe and efficacious in large case series in a variety of settings and patients. Ketamine has also proven safe and efficacious when compared to other agents for procedural sedation. This is the first randomized clinical trial to directly compare Ketamine by the intramuscular route with the intravenous route. The primary theoretical concern with IM Ketamine is the potential for an adverse airway event requiring rapid intravenous access.

CLINICAL QUESTION: In children undergoing procedural sedation for fracture reduction in the emergency department does the route of administration of Ketamine (intravenous versus intramuscular) influence the efficacy, length of sedation and rate of adverse events?

DESIGN/VALIDITY: This is a well-designed randomized clinical trial that included 208 patients in the primary analysis. The primary validity concern is the potential inequality of Ketamine dosing used in the study. The study began using dose supported by the literature (1 mg/kg IV vs 4 mg/kg IM). However, 25% in the IV group compared to 9% in the IM group required additional doses. It is difficult to assess efficacy and safety if nonequivalent dosages are utilized. It would have been helpful to know the length of the procedure. Intravenous doses repeated for a long procedure would be interpreted differently than additional intravenous dose given for inadequate sedation during a short procedure.

PRIMARY RESULTS: In terms of efficacy, the IM group demonstrated significantly less pain during the procedure and required additional dosages less often. In terms of safety, there were less respiratory adverse events in the IM group (Absolute Risk Difference: IV (11%) – IM 4% = 7% (0.5, 14.6%). Though the difference was statistically significant it did not reach the 10% difference that the authors considered clinically significance. The number needed to treat is 1/ARD = 1/0.07 = 14 for any adverse respiratory event. 14 patients would need to be treated with IM compared to IV Ketamine to prevent 1 additional adverse respiratory event. 2 (0.9%) patients required bag-valve mask ventilation and none required endotracheal intubation.

There was no adverse effect in the IM group required subsequent IV placement. However, there was more emesis and increased length of sedation in the IM group. The increased emesis and longer length of stay did not result in a difference in parental satisfaction.

APPLICABILITY: The study results are likely generalizable to patients in the ED setting meeting the studies inclusion and exclusion criteria.

AUTHOR'S CONCLUSION: "In summary, we found that pediatric patients administered Ketamine 4 mg/kg IM had lower self-reported pain and lower observed distress scores during the painful procedure than those receiving Ketamine 1 mg/kg intravenously. However, patients receiving Ketamine intramuscularly were also more likely to vomit in the emergency department, as well as at home, and experienced a longer length of sedation than those who received Ketamine intravenously. We found no difference in respiratory adverse events or parental or guardian and physician satisfaction of sedation between groups."

POTENTIAL IMPACT: This study supports the safety of IM Ketamine but with some tradeoffs. IM therapy led to significantly less self-reported pain during orthopedic reduction, and a statistically but not clinically significantly lower rates of respiratory adverse events compared to IV therapy. There were no adverse event in the IM group requiring IV insertion though the sample size makes limits conclusions about rare adverse events. The presence of and respiratory adverse events highlights the need for having personnel trained in the identification and management of pediatric adverse airway events and who are not directly involved in the procedure. Potential drawbacks to IM Ketamine include a significantly longer recovery time and to increased rates of emesis.

PROCEDURAL SEDATION: ONDANSETRON WITH KETAMINE

In children receiving intravenous Ketamine for procedural sedation does the addition of intravenous Ondansetron when compared to Placebo decrease the rate of emesis in the emergency department and after discharge?

Kelly Cleary M.D., Jeff Fine M.D.
May 2010

Langston WT, Wathen JE, Roback MG, Bajaj L.

EFFECT OF ONDANSETRON ON THE INCIDENCE OF VOMITING ASSOCIATED WITH KETAMINE SEDATION IN CHILDREN: A DOUBLE-BLIND RANDOMIZED, PLACEBO-CONTROLLED TRIAL.

Ann Emerg Med. 2008 Jul;52(1):30-4.
PubMed: 18353503

STUDY DEFINITIONS	
POPULATION	Inclusion: 1-18 years, ASA class 1 or II (healthy or with mild systemic disease), intravenous Ketamine for an emergency department procedure. Exclusion: Concurrent vomiting, previous adverse reaction to Ketamine or Ondansetron, Ketamine contraindications (hypertension, glaucoma, acute globe injury, increased intracranial pressure, central nervous system mass lesion, major psychiatric disorder, porphyria) Setting: Single Children's Hospital ED, 1/2003-8/2005
INTERVENTION	Ketamine 1 mg/kg (max dose 100 mg) + Ondansetron 0.15 mg/kg (max 4 mg)
CONTROL	Ketamine 1 mg/kg (max dose 100 mg) + Placebo (2 ml of normal saline)
CO-INTERVENTIONS	Glycopyrrolate 5 mcg/kg (max dose 250 mcg) Additional doses of Ketamine at MD discretion
OUTCOME	Primary Outcome: Vomiting in the ED and within 12 hours of discharge Secondary Outcomes: Length of ED stay: From initial ketamine dose until ED discharge Discharge criteria: 1. Airway patent with adequate oxygenation 2. Awake or easily aroused; minimal tactile/vocal stimulation may be necessary. 3. Swallowing reflex present, ability to swallow clear liquids protect the airway 4. Pre-sedation level of responsiveness achieved. Vancouver Sedation Recovery Scale ≥ 8 or higher Patient or parent's satisfaction
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized by a computer generated random-number table, supplied by a statistician, within blocks of 8 and within strata determined by fasting status (≤ 6 hours and vs. > 6 hours).
Was randomization concealed?	Yes. The study drug order was sent to the pharmacy where the randomization schedule was located. The pharmacist prepared the study drug syringe in a nondescript syringe that was sent back to the ED labeled as “sedation study drug.”
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Patients were similar in most characteristics. There was a 10% (14 patients) higher percentage of males in the Ondansetron group though it is unlikely to influence the study outcomes.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The medical staff, parents, and patients were blinded to the contents of the “sedation study drug” syringe.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes and No. Follow up was complete for the emergency department outcome of emesis. For emesis after discharge 87% (111/128) completed phone follow up in the Ketamine and Ondansetron group and 79% (100/127) completed phone follow up in the Ketamine and Placebo group
Were patients analyzed in the groups to which they were randomized?	Yes. An intention to treat analysis was conducted though not explicitly stated in the article (See Figure1: CONSORT diagram) The analysis excluded those who withdrew, went to the operating room or never received sedation.
Was the trial stopped early?	No. The trial was not stopped early.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

	EMESIS IN THE ED		
	YES	NO	
PLACEBO	16	111	127
ONDANSETRON	6	122	128
	18	233	255

Primary Outcome: Emesis in the ED
Prevalence: 18/255 = 7.1%
Risk Placebo: 16/127 = 12.6%
Risk Ondansetron: 6/128 = 4.7%
Risk Difference = AR Placebo–AR Ondansetron = 12.6% - 4.7% = 7.9%, 95% CI (1.1, 14.7%)

The authors considered a 12% difference to be clinically significant in their sample size determination.

Subgroup Analysis: ≥ 5 years:
Risk Difference: Risk Placebo - Risk Ondansetron
= 18.8% - 6.3% = 12.5%, 95% CI (2.8, 22.7%)

Secondary Outcomes:
Length of ED stay (minutes):
Ketamine + Ondansetron: 90.6 minutes
Ketamine + Placebo: 97.3 minutes
Risk Difference: -6.7 minutes, 95% CI (-18.1, 5.1)

No clinically apparent pulmonary aspiration

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

There is a wide confidence interval (CI) for the absolute risk difference reflecting the low prevalence of vomiting in the study.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. The study patients were similar to our patients with respect to age. However, ethnicity is not reported. Also, all patients received intravenous Ketamine, and there are instances where intramuscular Letamine is used as well in our emergency department.
Were all patient important outcomes considered?	Yes. The authors considered emesis both in the ED and after discharge, length of emergency department stay, and parental satisfaction.
Are the likely treatment benefits worth the potential harm and costs?	Likely Yes. Risk difference for the primary outcome was 7.9%, 95% CI (1.1, 14.7%). This was statistically significant but not clinically significant by the authors criteria. The number need to treat (1/ARD = 1/0.079) is 13. For every 13 patients treated with Ondansetron, 1 additional patient would not have emesis. The confidence interval for the NNT is wide. At the upper limit 91 patients would need to be treated before 1 additional patient benefits from the ondansetron). However, ondansetron is inexpensive (< $10/ dose) and has a relatively safe side effect profile. Therefore, an argument can be made that the benefits may be worth the risks and costs.

CLINICAL BOTTOM LINE

BACKGROUND: Ketamine has many properties that make it a safe and effective for procedural sedation in pediatric patients. However, emesis is a common side effect of Ketamine use (between 10 and 20% in the study institution). Emesis during the sedation period may increase the risk of pulmonary aspiration. Emesis after the sedation period can increase the time to full recovery and emergency department length of stay. Emesis after emergency department discharge may provoke anxiety for parents and require an unscheduled return visit if emesis is persistent.

CLINICAL QUESTION: In children receiving intravenous Ketamine for procedural sedation does the addition of intravenous Ondansetron when compared to Placebo decrease the rate of emesis in the emergency department and after discharge?

DESIGN/VALIDITY: This study was a well-designed randomized, double-blind placebo, controlled trial with including 255 patients in the primary analysis. This was a convenience sample raising the possibility selection bias. In addition, because of loss to follow up, the rate of post discharge emesis may be underestimated.

PRIMARY RESULTS: The authors report that patients receiving Ketamine and Ondansetron have a lower rate of vomiting in the ED and after discharge (Table 3) than those receiving Ketamine and a Placebo. Patients in the Ondansetron group were 7.9% less likely to have emesis as compared to those in the placebo group (Risk Difference: 7.9%, 95% CI (1.1, 14.7%). While this is a clinically significant difference, the authors considered a 12% difference to be clinically significant in their sample size determination.

In a subgroup analysis of those greater than or equal to 5 years of age, who have a higher rate of vomiting, the absolute the Risk Difference is 12.5%, 95% CI (2.8, 22.7%). This is both statistically significant and clinically significant by the authors criteria.

The number need to treat to prevent 1 additional patient from vomiting is 13, 95%CI (7, 91). For every 13 patients treated with Ondansetron, 1 additional patient would not have emesis compared to Placebo. The confidence interval is wide. At the upper limit 91 patients would need to be treated before 1 additional patient benefits from the Ondansetron. The number need to treat to prevent 1 additional patient from vomiting greater than or equal to 5 years of age is 8, 95% CI (5, 34).

The was no statistically significant difference in the secondary outcomes of length or ED stay or patient or parent satisfaction. The study is not powered to determine the rare adverse events such as risk of pulmonary aspiration that can be associated with vomiting.

The authors report that patients receiving ondansetron have a lower rate of vomiting in the ED and after discharge (Table 3). However, the outcomes assessed were emesis in the ED and in the ED and after discharge. A separate analysis of those only vomiting after discharge would have been helpful. It also may have been helpful to determine that effect of Ondansetron on those receiving more than one dose of Ketamine. Though randomization was stratified by fasting status (≤ 6 hours and vs. > 6 hours), no results were reported for these subgroups.

APPLICABILITY: The study results are likely generalizable to those meeting the study's inclusion and exclusion criteria. The study results may not be applicable to those receiving intramuscular Ketamine which has been associated with a higher rate of emesis and may not be applicable to those receiving doses greater than 1 mg/kg of Ketamine intravenously. The efficacy or orally administered Ondansetron, particularly in those receiving Ketamine intramuscularly cannot be determined from this study.

AUTHOR'S CONCLUSION: "In summary, we found that children administered intravenous ondansetron before intravenous ketamine experienced a significantly reduced incidence of vomiting. Because the administration of ondansetron did not significantly affect length of Emergency Department stay or parental satisfaction with sedation and the number of patients needed to treat to prevent a single episode of vomiting was relatively high, the clinical applicability of this practice remains in question. Patients aged 5 years and older may benefit the most from the intervention. As the cost of ondansetron decreases, those sites that experience higher rates of vomiting may consider pretreatment with ondansetron with ketamine, especially for children aged 5 years and older."

POTENTIAL IMPACT: It seems reasonable to consider giving Ondansetron prophylactically to prevent emesis as it is relatively inexpensive with fever adverse effects. This may be especially true for those greater than 5 years of age who demonstrated a higher risk of vomiting then the group as a whole and a greater reduction in vomiting with Zofran. However, there was no difference in the secondary outcomes of emergency department length of stay or patient or parent satisfaction.

PROCEDURAL SEDATION: FASTING STATUS (PROSPECTIVE)

In pediatric patients undergoing procedural sedation for painful procedures or imaging in the emergency department is the during of fasting or whether fasting guidelines are met associated with an increased risk of adverse events?

Michael Mojica, M.D.
July 2017

Agrawal D, Manzi SF, Gupta R, Krauss B.

PREPROCEDURAL FASTING STATE AND ADVERSE EVENTS IN CHILDREN UNDERGOING PROCEDURAL SEDATION AND ANALGESIA IN A PEDIATRIC EMERGENCY DEPARTMENT

Ann Emerg Med. 2003 Nov;42(5):636-46.
PubMed ID: 14581915

STUDY DEFINITIONS	
POPULATION	Inclusion: Patients requiring sedation for painful procedures or diagnostic imaging. Use of intravenous, intramuscular, oral, rectal, or inhalational agents. Emergency attending physicians and fellows performed all sedations in accordance with Joint Commission on Accreditation of Healthcare Organizations guidelines and departmental procedural sedation and analgesia protocols. Mandated by hospital-wide policy to record all adverse events on the sedation monitoring record. Exclusion: 1. Patients receiving medications for endotracheal intubation, muscle spasms, anxiolysis, rapid tranquilization for psychiatric agitation, seizure control, intractable vomiting, hiccups, or pain control without an associated procedure 2. Patients with no dietary history documented were excluded from analysis of the relationship between fasting status and adverse events. Setting: Single, Pediatric ED, 8-10/2001, 2-9/2002
EXPOSURE	Non-Compliance with ASA/AAP sedation guidelines: Fasting duration for either solids OR clear liquids was less than the recommended duration. Solids: Non-clear liquids such as infant formulas, breast milk, nonhuman milk. Clear Liquids: Water, fruit juices, carbonated beverages, clear tea, black coffee.
CONTROL	Compliance: Fasting duration for both solids AND clear liquids met recommendations (See Appendix)
OUTCOME	TYPE I ADVERSE EVENTS Apnea Airway misalignment requiring repositioning Bronchospasm Cardiovascular instability Emergence reactions Emesis Laryngospasm Oxygen desaturation less < 90% Paradoxical reactions Pulmonary aspiration Stridor TYPE II ADVERSE EVENTS* Reversal of sedation Hospital admission Endotracheal intubation Permanent neurological injury Death *Complications that negatively affected outcome, delayed recovery, or resulted in actual harm to the patient. Inadequate sedation or prolonged sedation without associated complication was not considered an adverse event.
DESIGN	Observational: Prospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?

ASIDE FROM THE EXPOSURE OF INTEREST DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or did statistical adjustments address the imbalance).	Unclear. Table 2 (Medications), Table 3 (Indications) and Table 4 (Adverse events) provide the demographic characteristics of the population. There is no description of the demographic characteristics comparing those who met and who did not meet fasting criteria.
Were the circumstances and methods for detecting the outcome similar?	Yes. Adverse events were clearly defined and were abstracted from sedation forms that were completed as part of the medical record.
Was follow-up sufficiently complete?	Yes. Adverse events that occurred prior to discharge were documented on ED sedation monitoring forms. Adverse events that could have occurred after discharge such as emergence reactions and vomiting were not assessed.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

N = 1,014, median age 5.4 years

ASA Class: I (77%), II (19%), IIII (4%), IV (0%), V (0%)

Medications:
Ketamine ± Versed (46.7%)
Fentanyl/Versed (23.2%), Chloral hydrate (12.3%)

Indications:
Fracture/dislocation (39.8%)
Imaging (25%)
Laceration repair (17.1%)
Lumbar puncture (4.0%)

Fasting Status
905/1,014 (89%) with fasting status documented
Fasting Compliant: 396/905 = 44%, 95% CI (39, 49%)
Fasting Non-Compliant: 509/905 = 56%, 95% CI (53,60%)

Adverse Events (See table in Clinical Bottom Line)
68/1,014 = 6.7%, 95% CI (5.2, 8.4%)
Fasting Compliant AE: 8.1%, 95% CI (5.6, 11.2%)
Fasting Non-compliant AE: 6.9%, 95% CI (4.8, 9.4%)
Risk Difference: 1.2%, 95% CI (-2.2, 4.8%).
The authors defined a 6% difference in adverse event rate between fasting compliant and fasting noncompliant patients as clinically significant in their sample size determination.

HOW PRECISE IS THE ESTIMATE OF THE RISK?

The 95% confidence interval for the difference in adverse events in fasting complaint and fasting non-compliant patients (1.2%, 95% CI (-2.2, 4.8%)) was narrow, not statistically significant and less than what the authors considered clinically significant.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Yes. Patients undergoing a variety of different procedures with a variety of medications were included.
Was follow-up sufficiently long?	No. Adverse events that could have occurred after discharge such as emergence reactions and vomiting were not assessed.
Is the exposure similar to what might occur in my patient?	Unclear. Ketamine ± Midazolam (23.4%) was the most common medication regimen used in the study. Ketamine is no longer used with Midazolam to prevent emergence reactions. Chloral Hydrate (12.3%) and Pentobarbital (11.8%) are no longer used as well. Other medications to study include: Midazolam alone, Etomidate and Precedex.
What is the magnitude of the risk?	The difference in adverse events in fasting compliant and fasting non-compliant patients (1.2% (-2.2, 4.8%)) was small, not statistically significant and not clinically significant by the authors criteria.
Are there any benefits that offset the risks associated with exposure?	The primary benefit in not meeting time to sedation guidelines is the ability to perform procedural sedation when it is most appropriate for the patient and to avoid unnecessary delays.

CLINICAL BOTTOM LINE

BACKGROUND: Fasting guidelines have been developed to decrease the risk of adverse events in patients undergoing surgery. These guidelines have been extrapolated to patients undergoing procedural sedation in settings other than the operating room without significant evidence supporting their use. One major difference is that operative patients typically have an airway intervention (endotracheal intubation, laryngeal mask airways) and paralysis. This puts them at a significantly higher risk of airway related adverse events. In the emergency department setting it is not always practical to delay procedures to meet fasting guidelines. The association of fasting status and adverse events in children undergoing procedural sedation for non-elective procedures in the pediatric emergency department has not been established.

CLINICAL QUESTION: In pediatric patients undergoing procedural sedation for painful procedures or imaging in the emergency department is the during of fasting or whether fasting guidelines are met associated with an increased risk of adverse events?

DESIGN/RISK OF BIAS: This was a well-designed prospective cohort study that included 1,014 patients who underwent procedural sedation in the emergency department 905 (89%) of whichhad documented fasting status. There is no description of the demographic characteristics comparing those who met and who did not meet fasting criteria. Adverse events that occurred prior to discharge were documented on ED sedation monitoring forms. Adverse events that could have occurred after discharge such as emergence reactions and vomiting were not assessed. The study would have benefited from a regression analysis to control for the effects of multiple confounding variables and identify independent predictors or adverse events.

PRIMARY RESULTS: 96% of patients were ASA Class I or II (ASA I (77%), II (19%), IIII (4%), IV (0%), V (0%)). The most common medications used were: Ketamine ± Versed (46.7%), Fentanyl/Versed (23.2%) and Chloral hydrate (12.3%). The most common indications were: fracture/dislocation (39.8%), imaging (25%), laceration repair (17.1%), lumbar puncture (4.0%) and abscess incision and drainage (3.6%).

68/1,014 (6.7%, 95% CI (5.2, 8.4%)) of patients had an adverse event. 77 adverse events occurred in 68 patients. Adverse events occurred more frequently in older ages and at a higher depth of sedation. There was no association between the medication used or indication for use and the risk of adverse events. Of the 15 patients who vomited, only 1 vomited during the procedure. There was not clinical evidence of aspiration pneumonia (0% 95% CI (0, 0.4%)). There was no significant difference in duration of sedation in those with and without adverse events. All adverse events were successfully managed with supplemental oxygen, airway repositioning, bag-valve mask ventilation, stimulation, suctioning or intravenous fluids. The study was underpowered to determine the difference in rare adverse events such as pulmonary aspiration.

905/1,014 (89%) of patients had fasting status documented. 56%, 95% CI (53, 60%) did not meet fasting guideline recommendations. The median and interquartile range of time to sedation for solids was 6.8 hours (4.9, 9.4) and for clear liquids 6.0 hours (3.9, 8.2). The duration of fasting was longest for both solids and clear liquids in the greater than 36-month age group and for those meeting sedation guidelines.

TYPE I ADVERSE EVENTS (PER PATIENT)			
Oxygen saturation less < 90%	32/1,014 (3.2%)	Cardiovascular instability	3/1,014 (0.3%)
Apnea	13/1,014 (1.3%)	Paradoxical reactions	4/1,014 (0.4%)
Stridor	0/1,014 (0%)	Emergence reactions	4/1,014 (0.4%)
Airway requiring repositioning	3/1,014 (0.3%)	Emesis	15/1,014 (1.5%)
Laryngospasm	2/1,014 (0.2%)	Pulmonary aspiration	0% (0, 0.4%)
Bronchospasm	0/1,014 (0%)		

There was no statistically significant difference in adverse events for those meeting fasting guidelines (8.1%, 95% CI (5.6, 11.2%)) and those not meeting fasting guidelines (6.9%, 95% CI 4.8, 9.4%)), Risk Difference: 1.2%, 95% CI (-2.2, 4.8%). The authors defined a 6% difference in adverse event rate between fasting compliant and fasting noncompliant patients as clinically significant in their sample size determination.

APPLICABILITY: The inclusion of multiple sedation agents, both procedural and imaging sedations and the inclusion of ASA Class I, III and III patients likely makes the study's results generalizable to most pediatric emergency department patients meeting the studies inclusion and exclusion criteria. 24% of patients received either Chloral hydrate or Pentobarbital which are both agents that are not used currently. On 14 patients were less then 6 months of age limiting the study's applicability to this age cohort.

AUTHOR'S CONCLUSION: "In summary, we performed a large-scale study of emergency department procedural sedation and analgesia that characterizes fasting status and assesses the relationship between preprocedural fasting state and adverse events. Our findings demonstrate that 56% of patients who were sedated had not fasted in accordance with established fasting guidelines for elective procedures. Despite the fact that these patients were not fasted for the appropriate duration (as defined by the fasting guidelines), they did not have any additional adverse events, including emesis. Noncompliance with the American Academy of Pediatrics/American Society of Anesthesiologists preprocedural fasting guidelines does not appear to be a contraindication to emergency department procedural sedation and analgesia.

This study provides further evidence that procedural sedation and analgesia practiced by pediatric emergency physicians as described in this study (medication regimens [Table 2], indications [Table 3] standardized presedation assessment, standardized post sedation discharge criteria, and lack of formal fasting guidelines) is safe and results in a low adverse event rate with no serious complications."

POTENTIAL IMPACT: The primary benefit in not meeting time to sedation guidelines is the ability to perform procedural sedation when it is most appropriate for the patient and to avoid unnecessary delays. This and other studies have not demonstrated an association between fasting status and adverse events in pediatric patients undergoing procedural sedation in the emergency department. The study was underpowered to find a significant difference in rare adverse events such as pulmonary aspiration. The 6.7% adverse event rate highlight the importance of close monitoring and personnel trained to manage pediatric airway difficulties.

The most recent American Academy of Pediatrics Guidelines (AAP) and The American College of Emergency Physicians (ACEP) Clinical Policy make conflicting recommendations.

The American College of Emergency Physicians (ACEP)
Clinical Policy on Procedural Sedation and Analgesia in the Emergency Department (WEB LINK) “Do not delay procedural sedation in adults or pediatrics in the ED based on fasting time. Preprocedural fasting for any duration has not demonstrated a reduction in the risk of emesis or aspiration when administering procedural sedation and analgesia (Level B recommendation, 2014)”

American Academy of Pediatrics (AAP)
Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures: Update 2016 (WEB LINK)
“Agents used for sedation have the potential to impair protective airway reflexes, particularly during deep sedation. Although a rare occurrence, pulmonary aspiration may occur if the child regurgitates and cannot protect his or her airway. Therefore, the practitioner should evaluate preceding food and fluid intake before administering sedation. It is likely that the risk of aspiration during procedural sedation differs from that during general anesthesia involving tracheal intubation or other airway manipulations. However, the absolute risk of aspiration during elective procedural sedation is not yet known; the reported incidence varies from ~1 in 825 to ~1 in 30,037. Therefore, standard practice for fasting before elective sedation generally follows the same guidelines as for elective general anesthesia; this requirement is particularly important for solids, because aspiration of clear gastric contents causes less pulmonary injury than aspiration of particulate gastric contents.”

SEE ALSO:

Beach ML, Cohen DM, Gallagher SM, Cravero JP.
Major Adverse Events and Relationship to Nil Per Os Status in Pediatric Sedation/Anesthesia Outside the Operating Room: A Report of The Pediatric Sedation Research Consortium.
Anesthesiology. 2016;124(1):80-88., PubMed ID: 26551974

APPENDIX: FASTING GUIDELINES

AAP/ASA GUIDELINES: PRE-PROCEDURAL FASTING FOR ELECTIVE PROCEDURES		
AGE	SOLIDS/NON-CLEAR LIQUIDS*	CLEAR LIQUIDS
< 6 months	4-6 hours (AAP 4 hours)	2 hours
6-36 months	6 hours	2 hours
> 36 months	6-8 hours (AAP 8 hours)	2 hours
*Infant formulas, breast milk and non-human milk		

PROCEDURAL SEDATION:
PRE-PROCEDURAL FASTING (RETROSPECTIVE)

In children requiring non-elective, intravenous or intramuscular procedural sedation in the emergency department is length of pre-procedural fasting associated with a risk of adverse respiratory events and vomiting?

Kevin Ching M.D., Michael Tunik M.D.

December 2004

Roback MG, Bajaj L, Wathen JE, Bothner J.

PREPROCEDURAL FASTING AND ADVERSE EVENTS IN PROCEDURAL SEDATION AND ANALGESIA IN A PEDIATRIC EMERGENCY DEPARTMENT: ARE THEY RELATED?

Ann Emerg Med. 2004 Nov;44(5):454-9.
PubMed ID: 15520704

STUDY DEFINITIONS

POPULATION	Inclusion: Sedation in ED by ED physicians (Propofol, Methohexital, Chloral Hydrate not used) Exclusion: 1. Sedation in the ED by pulmonary physicians for bronchoscopy 2. Sedation by the oral or intranasal route Setting: Single Children's Hospital ED, 6/1996-3/2003
EXPOSURE	Data collected from standardized sedation form completed by nurses Fasting: 0-2 hours, 2-4 hours, 4-6 hours, 6-8 hours, > 8 hours, not documented Time of last oral intake for food, milk and clear liquids.
OUTCOME	Primary Outcome: Adverse events: 1. Respiratory: apnea, laryngospasm, desaturations (< 90% room air), aspiration. 2. Vomiting
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?

ASIDE FROM THE EXPOSURE OF INTEREST DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or did statistical adjustments address the imbalance).	No. Demographic characteristics, the nature of the procedure, pre-procedural risk factors (e.g. ASA classification) and the nature and dosing of the sedatives used were not documented for each category of fasting time analyzed. The exposure (duration of fasting) was analyzed as a categorical variable. The nature and volume of intake were not consistently documented. 20% of patients did not have fasting time measured. The demographic characteristics (Table 1) and risk of adverse events (Table 4) were not significantly different in patients with undocumented fasting times.
Were the circumstances and methods for detecting the outcome similar?	Unclear. The outcomes (adverse events) were clearly defined and were measured by the nurses and physicians caring for the patients and recorded onto standardized sedation sheets. These sheets were analyzed retrospectively and were not designed for study purposes so that potential adverse events may have been undocumented. Outcome assessors were not blinded to fasting time.
Was follow-up sufficiently complete?	Yes. All patients were followed to ED discharge or admission. Short term events were unlikely to be missed. Long term adverse events mere not measured.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

N = 2,085
Mean age: 6.7 years
Procedure: Fracture reduction (53%), Laceration (20%)

ADVERSE EVENTS	14.8%
Desaturation (165)	8.1%
Apnea (16)	0.8%
Laryngospasm (2)	0.1%
Aspiration (0)	0.0%
Vomiting (156)	7.5%

MEDICATION	RESP	VOMITING
Ketamine* (1,199)	5.8%	10.8%
Ketamine*/Midazolam (295)	9.5%	5.4%
Fentanyl/Midazolam (284)	19%	1.4%
Midazolam (225)	5.8%	0.9%
Midazolam/Morphine (29)	10.3%	0.0%
Other (53)	7.4%	9.4%
*Both intravenous and intramuscular Ketamine		

	ANY ADVERSE EVENT	ODDS RATIO (95% CI)
0-2 hours (150)*	12%	1
2-5 hours (391)	16.4%	1.44 (0.82, 2.51)
4-6 hours (430)	14.0%	1.19 (0.68, 2.09)
6-8 hours (281)	14.6%	1.25 (0.69, 2.27)
> 8 hours (303)	14.5%	1.25 (0.69, 2.24)
Unknown (530)	15.5%	1.34 (0.78, 2.32)
*Reference standard (odds ratio denominator)		

HOW PRECISE IS THE ESTIMATE OF THE RISK?

The 95% confidence intervals for the odds ratios indicate that there was no statistically significant difference in the rate of any adverse event for any time interval when compared to the rate at 0-2 hours. There was also no statistically significant difference when respiratory adverse events and vomiting were analyzed independently (Table 4).

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Unclear. Except for age and gender, little information was presented on patient demographics, morbidity, or other prognostic factors. The sedatives used and procedures completed are similar to those used in our practice.
Was follow-up sufficiently long?	No. Long term adverse events mere not measured thought it would be expected that respiratory adverse events would occur prior to discharge given the duration of sedative effects. Vomiting may have occurred after discharge
Is the exposure similar to what might occur in my patient?	Yes. Ketamine is the most frequent agent used for procedural sedation in our institution. Midazolam alone or in combination with Ketamine, Fentanyl or Morphine are not used at our institution
What is the magnitude of the risk?	The study did not reveal an association between fasting time and adverse events. Power was insufficient to determine the association of duration of fasting with rare adverse events such as aspiration.
Are there any benefits that offset the risks associated with exposure?	Limiting the exposure (by increasing the duration of pre-procedural fasting) does not appear to reduce the incidence of adverse outcomes.

CLINICAL BOTTOM LINE

BACKGROUND: Guidelines for pre-procedural fasting for children have been established by several agencies. These guidelines were developed primarily for elective procedures and have been extrapolated to non-elective procedures despite a lack of evidence supporting their impact on patient safety. Importantly these guidelines were established for procedures requiring airway interventions such as endotracheal intubation and thus are aimed at patients who are at higher risk of a respiratory complication. These recommendations may not apply to patients undergoing procedural sedation without airway interventions.

CLINICAL QUESTION: In children requiring non-elective, intravenous or intramuscular procedural sedation in the emergency department is length of pre-procedural fasting associated with a risk of adverse respiratory events and vomiting?

DESIGN/RISK OF BIAS: This was a retrospective cohort study of data collected from standardized sedation forms that included 2,085 patients in the primary analysis. The primary validity concerns are related to the use or retrospective data collection. Fasting was not documented in 20% of patients and the distinction between oral and solid intake was not consistently available. Because of this, it was not possible to categorize patients into those meeting fasting guidelines and those who did not.

PRIMARY RESULTS: 14.5% (309/2,085) had adverse events. 8.7% (183/2,085) had a respiratory adverse event. The most common respiratory event was desaturation (8.1%). Apnea (0.8%) and laryngospasm (0.1%) occurred less frequently. No clinically apparent pulmonary aspiration was reported in this study, though the authors concede that a larger study population would likely be needed to determine the risk of aspiration.

Adverse events were not linked to shorter pre-procedural fasting times. The 95% confidence interval for the odds ratios indicate that there was no statistically significant difference in the rate of any adverse event for any time intervals when compared to the rate at 0-2 hours. There was also no statistically significant association when respiratory adverse events and vomiting were analyzed independently.

	ADVERSE EVENTS	ODDS RATIO (95% CI)	RESP	ODDS RATIO (95% CI)	VOMIT	ODDS RATIO (95% CI)
0-2 hr (150)	12%	1*	7.3%	1*	6.7%	1*
2-5 hr (391)	16.4%	1.44 (0.82, 2.51)	7.7%	1.05 (0.51, 2.15)	10.2%	1.60 (0.78, 3.28)
4-6 hr (430)	14.0%	1.19 (0.68, 2.09)	7.2%	0.98 (0.48, 2.00)	7.0%	1.05 (0.50, 2.20)
6-8 hr (281)	14.6%	1.25 (0.69, 2.27)	9.6%	1.34 (0.65, 2.79)	6.4%	0.96 (0.43, 2.13)
> 8 hr (303)	14.5%	1.25 (0.69, 2.24)	6.3%	0.85 (0.40, 1.80)	8.9%	1.37 (0.65, 2.91)
? (530)	15.5%	1.34 (0.78, 2.32)	10.2%	1.43 (0.73, 2.82)	5.8%	0.87 (0.42, 1.82)

GREEN = Statistically Significant, RED = Not Statistically Significant
*0-2 hours served as the reference standard (The odds ratio denominator)

APPLICABILITY: The study results are likely generalizable to pediatric patients receiving procedural sedation in the emergency department who meet the studies inclusion and exclusion criteria. However, the results may not be applicable to sedative agents such as Propofol or Methohexitol that were not used in the study and to sedation using the intra-oral or intra-nasal route.

AUTHOR'S CONCLUSION: "Published guidelines for preprocedural fasting exist despite lack of data to support their impact on patient safety. These guidelines are also difficult to implement and impractical in an ED setting. Our data support previously reported conclusions that emergency physicians provided safe procedural sedation and analgesia for pediatric procedures, regardless of preprocedural fasting times."

POTENTIAL IMPACT: This study's larger sample size and incidence of events permitted a greater opportunity to detect an association between pre-procedural fasting times and adverse outcomes. Published pre-procedural fasting guidelines may not apply to pediatric patients undergoing elective sedation in the emergency department. The prevalence of respiratory events highlights the need for personnel trained in the assessment and management of respiratory adverse events.

The most recent American Academy of Pediatrics Guidelines (AAP) and The American College of Emergency Physicians (ACEP) Clinical Policy make conflicting recommendations.

The American College of Emergency Physicians (ACEP)
Clinical Policy on Procedural Sedation and Analgesia in the Emergency Department (WEB LINK) "Do not delay procedural sedation in adults or pediatrics in the ED based on fasting time. Preprocedural fasting for any duration has not demonstrated a reduction in the risk of emesis or aspiration when administering procedural sedation and analgesia (Level B recommendation, 2014)"

American Academy of Pediatrics (AAP)
Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures: Update 2016 (WEB LINK)
"Agents used for sedation have the potential to impair protective airway reflexes, particularly during deep sedation. Although a rare occurrence, pulmonary aspiration may occur if the child regurgitates and cannot protect his or her airway. Therefore, the practitioner should evaluate preceding food and fluid intake before administering sedation. It is likely that the risk of aspiration during procedural sedation differs from that during general anesthesia involving tracheal intubation or other airway manipulations. However, the absolute risk of aspiration during elective procedural sedation is not yet known; the reported incidence varies from ~1 in 825 to ~1 in 30,037. Therefore, standard practice for fasting before elective sedation generally follows the same guidelines as for elective general anesthesia; this requirement is particularly important for solids, because aspiration of clear gastric contents causes less pulmonary injury than aspiration of particulate gastric contents."

SEE ALSO:

Agrawal D, Manzi SF, Gupta R, Krauss B.
Preprocedural Fasting State and Adverse Events in Children Undergoing Procedural Sedation and Analgesia in a Pediatric Emergency Department
Ann Emerg Med. 2003 Nov;42(5):636-46., PubMed ID: 14581915

PSYCHIATRY

1. Suicide and Depression: Attempt Prediction: PEC. 2015

DEPRESSION AND SUICIDE: SUICIDE ATTEMPT PREDICTION

In adolescents presenting for emergency psychiatric services does the Columbia Suicide Severity Rating Scale (C-SSRS) accurately distinguish those who will and will not return with a suicide attempt?

Michael Mojica, M.D.
May 2017

Gipson PY, Agarwala P, Opperman KJ, Horwitz A, King CA.

COLUMBIA-SUICIDE SEVERITY RATING SCALE: PREDICTIVE VALIDITY WITH ADOLESCENT PSYCHIATRIC EMERGENCY PATIENTS

Pediatr Emerg Care. 2015 Feb;31(2):88-94.
PubMed ID: 25285389

STUDY DEFINITIONS	
POPULATION	Inclusion: 13-17 years, presentation for emergency psychiatric services Exclusion: Patients not residing in county of presentation (to ensure capture of return visits) Setting: Single pediatric hospital, 10/2009-4/2010
RULE PARAMETERS	Columbia Suicide Severity Rating Scale interview conducted by social workers with video and in-person training. Time to conduct 1-10 minutes. Assesses suicidal ideation, the intensity of ideation and suicidal behavior (See Appendix).
CRITERION STANDARD	Each patient's medical records reviewed for 12 months after the index visit Return psychiatric emergency visits Return psychiatric emergency visits and suicide attempts at return visit
OUTCOME	Predictors of return psychiatric emergency visits Predictors of return psychiatric emergency visits for suicide attempts C-SSRS Intensity scale predictors of suicide attempts in those with suicidal ideation at index visit Suicidal Behavior: Defined as suicide attempts, aborted suicide attempts, interrupted suicide attempts, and preparatory suicidal actions. Suicidal Intent: Severity subscale score ≤ 3 indicates no intent, 4-5 indicates intent
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were the patients chosen in an unbiased fashion and do they represent a wide spectrum of severity of disease?	Yes. Patients were adolescents presenting for an emergency psychiatric evaluation for a variety of reasons and were well distributed by the C-SSRS Severity Scale at the index visit (Table 1). 47.8% did not endorse suicidal ideation in the week prior to the index visit.
Was there a blinded assessment of the criterion standard for all patients?	Unclear. It is unclear if those assessing a subsequent visit were aware of C-SSRS from the initial visit and what criteria were used to assess suicidality during the subsequent visit.
Was there an explicit and accurate interpretation of the predictor variables and the actual rule without knowledge of the outcome?	Yes. Social workers used a standardized data collection form to capture the elements of the C-SSRS. Temporally, this was completed at the index visit before any re-visit could have occurred.
Was there 100% follow up of those enrolled?	No. Medical records were reviewed for 12 months after the index visits. Patient living outside of the county were excluded. It is possible however that patients may have sought care elsewhere for subsequent visits and not have been included. 34.7% re-presented for emergency psychiatric services.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

N = 178, (Male 44%, Prior psych history 78%)
50.6% presented for suicidal ideation or attempt
30.4% with prior suicide attempt
10% with suicide attempt in the last week
34.7% (62/178) re-visit for psychiatric emergency visit
6.7% (12/178) with suicide attempt in the week prior

Rule characteristics (e.g. Sensitivity, Specificity) were not presented

Regression: Predictors of Re-visit
Past Psych Visit: Adjusted Odds Ratio1.52, 95% CI (1.08, 2.12)
Non-suicidal self-injury: Adjusted Odds Ratio: 2.19, 95% CI (1.09, 4.39)
C-SSRS Intensity Scale: Duration: Adjusted Odds Ratio 1.67, 95% CI (1.16, 2.42)

Regression: Predictors of Re-visit for Suicide Attempt
Non-suicidal self-injury: p = 0.04 (Adjusted Odds Ratio not presented)
Intensity Scale: Adjusted Odds Ratio 1.09, 95% CI (1.01, 1.17)
C-SSRS Intensity Scale: Duration: Adjusted Odds Ratio 1.80, 95% CI (0.88, 3.65)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

The potential impact of the rule could not be assessed with the data provided. The rule is an assistive and not a directive rule. The presence of any of the rule parameters does not direct the evaluator to a specific course of action. In the study, it is unclear in the what actions were taken based on the rule.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see Appendix)	☐ I ☐ II ■ III ☐ IV This is a level III rule. It has been validated in 1 narrow prospective sample. Use can be considered with caution and only in patients similar to the study population.
Does the rule make clinical sense?	Yes. It makes sense that prior psychiatric history, the intensity of suicidal ideation and suicidal behaviors are predictive of future return visits for suicidal behavior.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. The articles state that the social workers conducting the interview to assess the parameters of the C-SSRS underwent video and in person training. The duration of required training was not presented. The average time to conduct the survey was 1-10 minutes. No measure of inter-rater reliability was presented. It is unclear if non-psychiatric physicians could be trained to accurately assess the rule parameters.
Is the rule applicable to the patients in my practice?	Likely. However, approximately ¾ of patients were Caucasian and only 1/3 used government assisted insurance. This is distinctly different from our predominately Hispanic population. Resources to ensure follow up care are limited in our population. Subsequent psychiatric visits that were not for emergency psychiatric care were not described.
Will the rule results change my management strategy?	Not at present. It is our good fortune to have a separate pediatric psychiatric ED at Bellevue and the 24/7 availability of child psychiatry fellows and psychiatric social work
What are the benefits of applying the rule to my patients?	The rule could be used to target interventions to those at highest risk of subsequent suicidal behaviors.
What are the risks of applying the rule to my patients?	Given the paucity of psychiatric follow-up options there is a possibility that patients with a “positive” C-SSRS could be prioritized for follow-up care to the exclusion of other patients who could benefit more.

CLINICAL BOTTOM LINE

BACKGROUND: Suicide is the second leading cause of death in adolescents. Nearly 15% of high schools have strongly considered suicide. Many repeatedly attempt suicide and have been seen previously in the emergency department. The Columbia-Suicide Severity Rating Scale (C-SSRS) is a semi-structured clinical interview that assesses suicidal ideation severity, suicidal ideation intensity, and suicidal behavior. The authors state that “there is substantial momentum in the field to use the C-SSRS because it includes clearly defined categories of ideation and behavior that are largely consistent with the definitions recommended by the Centers for Disease Control and Prevention, and because the coordinated use of a single measure would enable the comparable measurement of suicidal thoughts and behaviors across sites and studies.”

CLINICAL QUESTION: In adolescents presenting to the ED for psychiatric services does the Columbia Suicide Severity Rating Scale (C-SSRS) accurately distinguish those who will and will not return with a suicide attempt?

DESIGN/RISK OF BIAS: This was a prospective validation of the Columbia-Suicide Severity Rating Scale (C-SSRS). The study was conducted at a single center and included 178 adolescents who presented for emergency psychiatric care of which approximately half presented for suicidal ideation or attempt and of which three quarters had a prior psychiatric history. The C-SSRS assesses suicidal ideation, the intensity of ideation and suicidal behavior.

One potential validity concern is that parameters not present in the rule but which had been shown to be predictive of future suicidal behavior were not consistently assessed so it could not be determined if the C-SSRS is predictive above that of regularly collected information. In addition, follow up was limited to a 12-month period after the index visit and was conducted by medical record review and not direct contact the patients, parents or the providers.

PRIMARY RESULTS: 34.7% (62/178) re-presented for a psychiatric emergency visit of which 6.7% (12/178) re-presented with suicide attempt in the week prior. Rule characteristics (e.g. sensitivity) were not provided and could not be calculated from the data presented. The results of two regression analysis were presented.

Three predictors were independently associated with a return emergency psychiatric visit. These included: a past psychiatric visit (aOR 1.52, 95% CI (1.08, 2.12), a history of non-suicidal self-injury (aOR: 2.19, 95% CI (1.09, 4.39) and a C-SSRS Intensity Scale: Duration item (aOR 1.67 (1.16, 2.42).

Three predictors were independently associated with a return emergency psychiatric visit for a suicide attempt. These included: a history of non-suicidal self-injury ($p = 0.04$ aOR not presented) the C-SSRS Intensity Scale (aOR 1.09, 95% CI (1.01, 1.17) and the C-SSRS Intensity Scale: Duration item (aOR 1.80 (0.88, 3.65). It is not clear from the data presented that the C-SSRS intensity scale would remain an independent predictor if the duration item was excluded.

The potential impact of the rule could not be assessed with the data provided. The rule is an assistive and not a directive rule. The presence of any of the rule parameters does not direct the evaluator to a specific course of action. It is unclear in the study what actions were taken based on the rule.

APPLICABILITY: The study results may not be readily generalizable to other populations. Approximately ¾ of patients were Caucasian and only 1/3 used government assisted insurance. This is distinctly different from our predominately Hispanic population. Resources to ensure follow up care are limited for our population. Subsequent psychiatric visits that were not for emergency psychiatric care were not described. It is likely that the availability of regular psychiatric follow-up would decreased the need for emergency psychiatric care. This is a level III rule. It has been validated in 1 narrow prospective sample. It could be considered for use with caution and only in patients similar to the study population.

AUTHOR'S CONCLUSION: "Psychiatric emergency service providers may use the C-SSRS in conjunction with other suicide risk assessment tools to aid with clinical decision-making. For instance, the data gathered from the C-SSRS may assist providers by identifying who may be more likely to return for psychiatric emergence care and who is most likely to return after a suicide attempt. Understanding and tailoring recommendations based on the information obtained at the index visit may help to prevent return psychiatric emergence visits. While we understand the difficulty of predicting at the individual level which adolescents will return for psychiatric care because of the diversity of factors that protect them from suicidal outcomes and place them at risk, the C-SSRS information may allow for more individual tailoring of treatment recommendations and practices, which in turn could have broader implications for healthcare use policy. Additionally, these efforts on the front end by psychiatric emergence providers could enhance the continuity of care allowing for richer clinical impressions shared with community-based providers who provide ongoing management of suicidal, non-suicidal self-injury behaviors and related mental health care for adolescents."

POTENTIAL IMPACT: The validity and applicability concerns discussed above limit the impact of the C-SSRS. For those without extensive psychiatric training the C-SSRS may provide as structure to the assessment of suicidality. The implications of the C-SSRS for specific interventions (e.g. more urgent or regular follow up care or pharmacologic management) have not been determined.

APPENDIX: COLUMBIA SUICIDE SEVERITY RATING SCALE

(WEB LINK: C-SSRS)

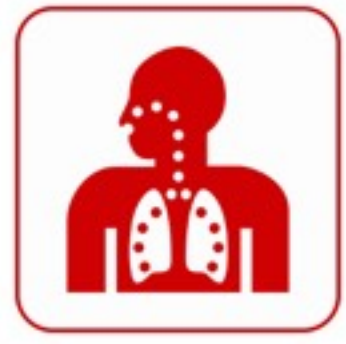
- Semi-structured Interview measuring the intensity of suicidal ideation and behavior
- Severity Sub-scale: 0 = no ideation, 1 wish to be dead, 5 suicidal intent with plan
  (Score ≤ 3 indicates no intent, 4-5 indicates intent)
- Intensity Sub-scale: 5 items: Frequency, duration, controllability, deterrents, reasons for ideation
  Ordinal scale: Total 2-25. Applied only to those with severity scale ≥ 1,
  A severity subscale of 0 results in an intensity subscale score of 0

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ.
The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings from Three Multisite Studies with Adolescents and Adults
Am J Psychiatry. 2011 Dec;168(12):1266-77., PubMed ID: 22193671

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

RESPIRATORY



1. Anaphylaxis: Glucocorticoids: J Pediatr. 2015
2. Asthma: Corticosteroid Timing: Ann Emerg Med. 2012
3. Asthma: High Dose Magnesium: Pediatr Crit Care 2016
4. Asthma: Nebulized Ipatropium: Pediatrics 1999
5. Asthma: Ketamine: Ann Emerg Med. 2005
6. Asthma: Magnesium Meta-Analysis: Arch Dis Child. 2005
7. Asthma: Metered Dose Inhalers: Pediatrics 2000
8. Asthma: Prednisone/Dex Meta-Analysis: Pediatrics 2014
9. Asthma: Single Dose Dexamethasone: Annals EM. 2016
10. Asthma: Terbutaline: Pediatr Emerg Care 2007
11. Bronchiolitis: Apnea Risk Factors: Annals EM. 2006
12. Bronchiolitis: Decompensation Risk: Hosp Peds 2017
13. Bronchiolitis: Epinephrine Dosing: N Engl J Med. 2013
14. Bronchiolitis: Epinephrine & Dex: NEJM 2009
15. Bronchiolitis: High Flow O2 Nasal Cannula: NEJM 2018

16. Bronchiolitis: Home Desaturations: JAMA Pediatr. 2016

17. Bronchiolitis: Hypertonic Saline: Arch Ped Adol. 2009

18. Bronchiolitis: Inpatient Epinephrine: N Engl J Med. 2003

19. Bronchiolitis: Noninvasive Ventilation: Lancet 2017

20. Bronchiolitis: Oral Dexamethasone: J Pediatr. 2002

21. Bronchiolitis: Oral Dex(PECARN): NEJM 2007

22. Bronchiolitis: Care Escalation (PERN): Pediatrics 2018)

23. Bronchiolitis: Pulse Oximetry at Discharge: JAMA 2014

24. Pneumonia: CRP : Pediatr Infect Dis J. 2008

25. Pneumonia: Leukocytosis: Pediatr Emerg Care. 2009

26. Pneumonia: POCUS: JAMA Pediatr. 2013

26. Pneumonia: POCUS Meta-Analysis: Pediatrics 2015

27. Pneumonia: POCUS Meta-Analysis: Ped Pulm 2018

27. Pneumonia: Tachypnea: Pediatr Infect Dis J. 2010

28.Pulmonary Embolism: PERC Validation: Annals EM. 2012

ANAPHYLAXIS: GLUCOCORTICOIDS

In pediatric patients with anaphylaxis, is glucocorticoid administration associated with a decreased length of stay for admitted patients or a decrease in emergency department re-visits within 3 days of presentation for discharged patients?

Alexis Pankow M.D., Laura Papadimitropoulos M.D.
January 2016

Michelson KA, Monuteaux MC, Neuman MI.

GLUCOCORTICOIDS AND HOSPITAL LENGTH OF STAY FOR CHILDREN WITH ANAPHYLAXIS: A RETROSPECTIVE STUDY.

J Pediatr. 2015 Sep;167(3):719-24.
PubMed ID: 26095285

STUDY DEFINITIONS	
POPULATION	Inclusion: Children age 1 month to 18 years who presented to the ED with a primary diagnosis of anaphylaxis Exclusion: Children with a previous ED visit within 3 days for a primary or secondary diagnosis of anaphylaxis and those with missing data Setting: Database from 35 tertiary care children's hospitals. 1/2009-9/2013
INTERVENTION	1 or more doses of Dexamethasone, Methylprednisolone or Prednisone/ Prednisolone intravenously or orally on the day of presentation
CONTROL	Patients with anaphylaxis who did not receive glucocorticoids
OUTCOME	Primary: Admitted patient: Prolonged length of stay ≥ 2 days for (a surrogate marker of biphasic anaphylaxis = symptoms > 6 hours or worsening after improvement) Discharged patient: ED Revisit within 3 days for an allergic reaction Secondary: Admitted patient: use of parenteral Epinephrine beyond the first hospital day.
DESIGN	Observational: Retrospective cohort

ARE THE RESULTS VALID?	
Was the sample of patient's representative?	Yes. Table 1 demonstrates the demographic information for the patients. This study occurred at 35 tertiary care children's hospital and included over 10,000 patients but there is a risk of referral bias and applicability to other setting is unclear.
Were the patients classified into prognostically homogeneous groups?	Yes. The two groups are compared in Table 1. There were more males in the discharged group who received glucocorticoids. The patients in the glucocorticoid group also received bronchodilators, Epinephrine and H1 or H2 blockers more often. Hospital transfers and central venous catheter rates were higher in the glucocorticoid group. These differences were noted in both the discharged and hospitalized patients. The differences in these characteristics were adjusted for in the regression analysis. A previous history of anaphylaxis or biphasic reactions was not obtained.
Was follow-up sufficiently complete?	Unclear. Data was available for all admitted patients until discharge There was no way to capture discharged patients who returned to another ED or office setting.
Were outcome criteria objective and unbiased?	The outcome of the study was prolonged length of stay ≥ 2 days for hospitalized patients and return ED visit within 3 days with an associated diagnosis of allergic reaction for discharged patients. Retrospective studies are at risk of record bias (required data not recorded). Prolonged length of stay was used because specific data on biphasic reactions was not available. In addition, the need for additional interventions at the unscheduled re-visit were not provided for discharged patients.

WHAT ARE THE RESULTS?

HOW LIKELY ARE THE OUTCOMES OVER TIME?

N = 10,225. 5,203/10,225 (50.7%) admitted

Adjusted Odds Ratio = (glucocorticoids/no glucocorticoids)

Length of Stay: Admitted Patients
8.2% (424/5,203) had a prolonged length of stay
Adjusted Odds Ratio: 0.61, 95% CI (0.41, 0.93)

Epinephrine after 1st Day: Admitted Patients
8.1% (422/5,203) had Epinephrine after the 1st day
Adjusted Odds Ratio = 0.63, 95% CI (0.48, 0.84)

ED Revisits within 3 days: Discharged Patients
4.9% (249/5,052) had a repeat ED visit
Adjusted Odds Ratio = 1.01, 95% CI (0.5, 2.05)

HOW PRECISE ARE THE ESTIMATES OF LIKELIHOOD?

Prolonged Length of Stay: The CI (0.41-0.93) for the adjusted OR did not include 1 indicating a statistically significant difference (decrease).

Epinephrine after 1st Day: The CI (0.48-0.84) for the adjusted OR did not include 1 indicating a statistically significant difference (decrease).

Revisits: The CI (0.5-2.05) for the adjusted OR did include 1 indicating that there is not a statistically significant difference (no change)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients and their management similar to those in my practice?	Unclear. The inclusion of 35 Children's hospitals likely makes population generalizable to other children's hospital ED. Applicability to other settings is unclear. The study population had a 51% admission rate, which is significantly higher than our admission rate. Glucocorticoids were used in 76% of admitted group and 67% of the discharge group, which is lower than our rate.
Was the follow-up sufficiently long?	Unclear. Follow up in 3 days is likely to identify the majority of discharged patients with biphasic reactions.
Can I use the results in the management of patients in my practice?	Unclear. We currently administer corticosteroids to all patients requiring admission and to the majority that are discharged.

CLINICAL BOTTOM LINE

BACKGROUND: Up to 20% of patients with anaphylaxis may have protracted symptoms or worsening symptoms after initial improvement (i.e. a biphasic reaction). Practice guidelines recommend corticosteroids as second line agents (after Epinephrine) in the treatment of anaphylaxis in order to mitigate potential biphasic reactions but acknowledge that there is little evidence and none from randomized clinical trials to support this recommendation.

CLINICAL QUESTION: In pediatric patients with anaphylaxis, is glucocorticoid administration associated with a decreased length of stay for admitted patients or a decrease in emergency department re-visits within 3 days of presentation for discharged patients?

DESIGN/VALIDITY: This was a retrospective study using a database representing 35 tertiary care children's hospitals. The study included 10,000 pediatric patients with anaphylaxis of which 50.7% were hospitalized. There are a number of bias risks in the design of this study. The primary outcome of prolonged length of stay is a surrogate marker of biphasic reaction and was arbitrarily dichotomized into less than or greater than or equal to 2 days. For the secondary outcome of return ED visit revisits, visits to other ED's or non-ED settings would have been missed and interventions required for those with a revisit were not presented. A variety of both intravenous and oral corticosteroids were administered. It is unclear if dosing was comparable or adequate and the duration of therapy was not provided.

PRIMARY RESULTS: Logistic regression was utilized to account for a long list of covariates (e.g. asthma history, anaphylaxis severity and underlying conditions). History of anaphylaxis or a history of biphasic reactions was not included. 54% of patients has concomitant asthma or a history of asthma and were included in the admitted cohort and 21% in the discharged cohort. These patients are more likely to receive and benefit from corticosteroids. A subgroup analysis excluding these patients would have been useful.

The prevalence of a prolonged length of stay (LOS) was 8.2% (249/5,203). The adjusted odds ratio for prolonged LOS (glucocorticoids/no glucocorticoids) was 0.61, 95% CI (0.41, 0.93). This indicates a statistically significant decrease in the odds of prolonged length of stay in those receiving glucocorticoids. Increasing age, a complex medical condition, history of asthma, oxygen use, bronchodilator use and ICU admission were also independent predictors of a prolonged length of stay. The secondary outcome of ED revisit with 3 days (glucocorticoids/no glucocorticoids) had an adjusted odds ratio of 1.01, 95% CI (0.5, 2.05). This indicates a non-statistically significant effect of corticosteroids on ED revisits.

APPLICABILITY: The inclusion of 35 Children's hospitals makes this population similar to other children's hospital Emergency Departments. Applicability to other settings is unclear. The study population had a 51% admission rate, which is significantly higher than our admission rate. It is unclear if this represents a sicker population (e.g. referral bias) or a lower threshold for admission. Glucocorticoids were used in 76% of admitted group and 67% of the discharge group, which is lower than our rate. The differences in these characteristics make it difficult to apply the study's results to our population.

AUTHOR'S CONCLUSION: "The use of glucocorticoids was inversely associated with prolonged LOS among children hospitalized with anaphylaxis, but was not associated with 3-day ED revisits among discharged children. These findings support the use of glucocorticoids in children hospitalized with anaphylaxis."

POTENTIAL IMPACT: The limitations in the study design, many inherent to the use of retrospective databases, make it unlikely that this studies result will lead to a change in current management strategies. Glucocorticoids have a low side effect profile when used for a limited time course and many physicians will likely to continue to use glucocorticoids for patients with anaphylaxis in both the inpatient and outpatient settings. This retrospective database study demonstrates the practice variation that exists in the use of corticosteroids and the need for more definitive randomized clinical trials.

ASTHMA EXACERBATION: CORTICOSTEROID TIMING

In children with a moderate to severe asthma exacerbation does an early (< 75 minutes from triage) when compared to a delayed administration of corticosteroids (> 75 minutes from triage) reduce the admission rate?

Maria Lame M.D., Michael Tunik, M.D.
December 2012

Bhogal SK, McGillivray D, Bourbeau J, Benedetti A, Bartlett S, Ducharme FM.

EARLY ADMINISTRATION OF SYSTEMIC CORTICOSTEROIDS REDUCES HOSPITAL ADMISSION RATES FOR CHILDREN WITH MODERATE AND SEVERE ASTHMA EXACERBATION.

Ann Emerg Med. 2012 Jul;60(1):84-91.
PubMed: 22410507

STUDY DEFINITIONS	
POPULATION	Inclusion: 2-17 years, acute asthma exacerbation, ≥ 1 Albuterol nebulizations in the ED, moderate or severe obstruction (baseline Pediatric Respiratory Assessment Measure (PRAM) score of 5-12 (See Appendix) Exclusion: Chronic illness (e.g., cystic fibrosis, bronchopulmonary dysplasia, cardiac or renal diseases), acute illness for which systemic corticosteroid was indicated (e.g. croup) or contraindicated (e.g., varicella), ongoing oral corticosteroids use on presentation. Setting: Single Children's Hospital, 9/2006-12/2006
INTERVENTION	Early administration (< 75 minutes of triage) of Prednisolone 1 mg/kg
CONTROL	Delayed administration (> 75 minutes of triage) of Prednisolone 1 mg/kg or No corticosteroids administered
OUTCOME	Primary Outcome: Admission: Hospital admission or > 6 hours between triage and the decision to admit or discharge. Secondary Outcomes: Length of active treatment: Time between first and last nebulization of Albuterol Relapse: A return visit to the ED for acute asthma within 72 hours of discharge
CO-INTERVENTIONS	Institutions Clinical Care Pathway: Recommends steroids within 60 minutes Moderate Asthma: ≥ 1 Albuterol nebulizations of 0.03 mL/kg 5% Albuterol) and Prednisone or Prednisolone (1 mg/kg; maximum 50 mg) Severe Asthma: 3 nebulizations of 0.03 mL/kg of Albuterol and 250 mcg Ipratropium Bromide, systemic corticosteroids (1 mg/kg of Prednisone or Prednisolone or 4-8 mg/kg of intravenous Hydrocortisone).
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)

ASIDE FROM THE EXPOSURE OF INTEREST DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or did statistical adjustments address the imbalance).	No. The early and late groups were assed prior to treatment and were similar in baseline health but not their current medical state. The early group had more acutely ill patients Triage Level 2: Early 52.7%, Late 13.9% PRAM > 8: Early 52.7%, Late 3.5% Cofounders that influenced the admission rate were accounted for by regression analysis.
Were the circumstances and methods for detecting the outcome similar?	Outcome was objectively defined as either hospital admission or a 6-hour delay before admission, measured from triage. Admission criteria were not detailed in the study. However, the methods for detecting outcome were same for both groups, which included duplicate data extraction. The healthcare providers managing the patients were unaware of the study being conducted, limiting potential bias.
Was follow-up sufficiently complete?	Yes. All patient included in the study had information extracted from the medical records. All included patients were followed through admission to discharge.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

Early: n = 205
Late: n = 201
N = 133 > 75 minutes, n = 68 no steroids in ED

<u>Primary Outcome: Admission or LOS > 6 hours</u>
Adjusted Odds Ratio (Early/Late): 0.4, 95% CI (0.2, 0.7)

<u>Length of Active Treatment</u>:
Risk Difference (Late – Early): 0.7 hours, 95%CI (0.8, 1.3)

<u>For every 30-minute delay in administration</u>:
Odds of Admission increase by 1.19, 95% CI (1.09, 1.35)
Duration of Active Treatment increased by 60 minutes (41, 80 minutes)

HOW PRECISE IS THE ESTIMATE OF THE RISK?

The confidence interval for the adjusted odds ratios are presented above

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Yes. The inclusion/exclusion criteria and patient characteristics appear similar to our population. The patients in the study may have had more severe asthma symptoms than our population given that only 21% had PRAM scores less than 4. Their clinical pathway for moderate asthmatics consisted of one or more Albuterol treatments plus Prednisolone 1 mg/kg. Severe asthmatics receive three treatments of Albuterol with Ipatropium plus corticosteroids. Ipatropium is used in our ED for moderate as well as severe exacerbations.
Was follow-up sufficiently long?	Yes. All patients were followed to the point of outcome. In addition, the emergency department records were reviewed to ensure all relapses presenting the same ED were recorded.
Is the exposure similar to what might occur in my patient?	Use of “standing orders” is limited by New York state. However, a standing policy of early admission of steroids might increase early steroid use.
What is the magnitude of the risk?	Those who received early corticosteroids were less than half as likely to be admitted.
Are there any benefits that offset the risks associated with exposure?	The primary benefit is the potential to decrease the rate of admission. A clinical pathway, with a validated Asthma score, used by all providers could ensure that patients for which corticosteroids are indicated receive them early. Clear criteria for administration would ensure that patients not requiring corticosteroids are not given them. The treatment benefits are worth the potential harm and costs given that patients with moderate to severe asthma symptoms, only the timing of corticosteroids would be altered. This should have no adverse effect on the patient. Earlier administration may be difficult depending on nursing/triage/physician availability, but overall costs should be justified by the reduced length of emergency department stay in patients who received earlier corticosteroids.

CLINICAL BOTTOM LINE

BACKGROUND: The NIH asthma guidelines recommend systemic corticosteroids for all patients who do not respond to therapy. Short courses of oral corticosteroids reduce the duration and may prevent hospitalizations and relapse following an acute exacerbation. This study examined the effects of the timing of the administration of corticosteroids in the treatment of moderate to severe asthmatics on admission rate and length of active emergency department therapy.

CLINICAL QUESTION: In children with a moderate to severe asthma exacerbation does the early (< 75 min) administration of corticosteroids reduce the admission rate?

DESIGN/RISK OF BIAS: This was a observational prospective cohort study that included 406 patients. The primary validity concerns stem from the fact that this was an observational cohort study and not a randomized clinical trial. Regression analyses were conducted to account for difference in those who received early or late corticosteroids. The primary outcome was admission or remaining in ED for more than six hours after triage. The need for admission was at the discretion of the treatment physician and explicit criteria for admission were not provided. Many factors are involved in the decision for admission including some that are not directly related to the severity of the asthma exacerbation or response to therapy. In addition, 34% of the “late” group did not receive any corticosteroids. This could potentially increase the apparent efficacy of early corticosteroids.

PRIMARY RESULTS: The study demonstrated that those treated early with steroids (< 75 minutes) had a decrease rate of admission (adjusted Odds Ratio (Early/Late): 0.4, 95% CI (0.2, 0.7). There was also a dose-response relationship between time to administration of corticosteroids and the rate of admission. For every 30 minutes delay in the administration of corticosteroids, the odds of hospital admission rose by 1.23, 95% CI (1.09,1.39) and the duration of active treatment increased by 60 minutes (95% CI, (41, 80 minutes).

APPLICABILITY: The study’s results are likely generalizable to those meeting the inclusion and exclusion criteria. In New York State triage nurses are not allowed to use standing orders for medication so a process of early notification of caregivers would be required.

AUTHOR’S CONCLUSION: “In this study of children with moderate or severe asthma, administration of systemic corticosteroids within 75 minutes of triage decreased hospital admission rate and length of active treatment, suggesting that early administration of systemic corticosteroids may allow for optimal effectiveness.”

POTENTIAL IMPACT: In patients with moderate to severe asthma who would be treated with corticosteroids, the study demonstrated a benefit to early administration. There are no apparent adverse events associated with early administration and there should be no reason not to implement this strategy in patients meeting criteria for corticosteroids. The reasons for a large proportion of patients not receiving corticosteroids in the 60 minutes recommended by the institutions clinical pathway needs to be addressed and is likely to some extent institution specific.

APPENDIX: PRAM SCORE

PEDIATRIC RESPIRATORY ASSESSMENT MEASURE (PRAM) SCORE		
CRITERION	DESCRIPTION	SCORE
Oxygen Saturation	≥ 95%	0
	92-94%	1
	< 92%	2
Suprasternal Retraction	Absent	0
	Present	2
Scalene Muscle Retraction	Absent	0
	Present	2
Air entry	Normal	0
	Decrease at the base	1
	Decrease at the apex and base	2
	Minimal or Absent	3
Wheezing	Absent	0
	Expiratory only	1
	Inspiratory with/without expiratory	2
	Audible without stethoscope or silent chest	3
Mild: 0-4, Moderate 5-8, Severe 9-12		

A change in PRAM of ≥ 3 points between 2 assessments corresponds to a 25% change in respiratory resistance. This is considered of a clinically meaningful improvement.

ASTHMA EXACERBATION: HIGH-DOSE MAGNESIUM INFUSION

In pediatric patients with severe asthma not responsive to conventional therapy in the Emergency department, does a high dose infusion of Magnesium sulfate when compared to standard dose bolus of Magnesium sulfate result in fewer admissions?

Kelsey Fawcett, MD., Dennis Heon, MD.
May 2016

Irazuzta JE, Paredes F, Pavlicich V, Domínguez SL.

HIGH-DOSE MAGNESIUM SULFATE INFUSION FOR SEVERE ASTHMA IN THE EMERGENCY DEPARTMENT: EFFICACY STUDY

Pediatr Crit Care Med. 2016 Feb;17(2): e29-33.
PubMed ID: 26649938

STUDY DEFINITIONS	
POPULATION	Inclusion: Patients ages 6-16 years old presenting to ED for severe asthma (as established by the Global Initiative Asthma Score) who failed to improve after 2 hours of standard therapy for asthma (Persistent signs of asthma including respiratory distress and a Woods-Downe's asthma score greater than 4) Exclusion: Underlying comorbidity or infectious etiology (Temp > 38.3C), antibiotics administered immediately prior or during ED visit Setting: Single Children's Hospital Pediatric ED (Paraguay). 10/2012-6/2014
INTERVENTION	Magnesium Sulfate: High dose MgSO4 Infusion (50 mg/kg/hour for 4 hours, max 8 grams/4 hours) diluted in 0.9% saline at a concentration of 10 mg/mL
CONTROL	Magnesium Sulfate: 50 mg/kg bolus (> 1 hour)
CO-INTERVENTIONS	Oxygen Dexamethasone 0.2 mg/kg IV Nebulized Salbutamol 5 mg every 20 minutes
OUTCOME	Primary Outcome: Discharge at 24 hours Secondary Outcomes: Total length of stay, cost implications
DESIGN	Interventional: Randomized Clinical Study

ARE THE RESULTS VALID?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized to receive either Magnesium Sulfate Bolus or Magnesium Sulfate Infusion by a previously prepared sealed envelope.
Was randomization concealed?	Partially. Patients were randomized by sealed envelopes to receive either Magnesium Sulfate Bolus or Magnesium Sulfate Infusion. While the initial treating physician may have been aware of whether or not the patient was received Magnesium Sulfate bolus or Magnesium infusion, the physician at the time of discharge was blinded to what the patient had received for treatment.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. The patients in the study groups were similar in age, sex, past medical history of asthma, initial asthma score at time of presentation to the ED, and initial Peak Flow Expiratory Rate (PEFR). The patients in the study group were also similar with respect to prognostic factors in that they were not obese patients, did not have significant underlying comorbid conditions, did not have suspected infectious etiology of wheezing, and did not receive antibiotics therapy prior to their ED visit. All patients received the same standardized asthma therapy including Dexamethasone 0.2 mg/kg IV and 5 mg of nebulized Salbutamol (max 5 mg) every 20 minutes in the first 2 hours of treatment. All patients in the study group after receiving the initial standardized treatment above had persistent signs of asthma including respiratory distress and a Woods-Downe's asthma score greater than 4.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded	The study was an open-label study and therefore the study was not blinded to the initial treating physician or to the patient. However, the treating physician at the time of discharge was blinded to the study group.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDY'S CONCLUSION?	
Was follow-up complete?	It is unclear whether or not follow-up was complete or how follow up was assessed. All patients were evaluated at 0 hours, 2 hours, and 6 hours post treatment using peak expiratory flow rate and assessing Asthma Score. Patient discharge rate was evaluated at 12, 24 and 36 hours post treatment. No patients returned to the ED within 1 week of treatment.
Were patients analyzed in the groups to which they were randomized?	Yes. The patients were analyzed in the groups to which they were randomized. Everyone was evaluated in the ED setting with the exception of 1 patient who was admitted to the hospital general ward (which typically would not occur in the management of asthma in the study institution). Despite this, the patient was included in the statistical analysis.

Was the trial stopped early	The trial was stopped early. The authors originally intended to enroll 44 patients based on their sample size determination. They completed an interim analysis and found that the difference was statistically significant so they stopped at a sample size of 38.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Primary Outcome:
Absolute Risk: MgSO4 Bolus: 2/19 = 10.5

PROPORTION DISCHARGED AT 24 HOURS

	DISCHARGED		
	YES	NO	
MgSO4 BOLUS	2	17	19
MgSO4 INFUSION	9	10	19
	11	27	38

Absolute Risk: MgSO4 Infusion (HDMI): 9/19 = 47%
Absolute Risk Difference (AR bolus – AR infusion)
10.5% - 47% = - 36.5%, 95% CI (10, 63%).

Secondary Outcomes:

Length of Stay:
HDMI 34.13 +/- 19.5 hours
Bolus 48.05 +/- 18.72 hours
Mean Difference = 13.9 hours, 95% CI (1.3, 26.5 hours)

Hospital Cost:
HDMI 603.16 +/- 338.47,
Bolus 834.37 +/- 306.73
P = < 0.016 (< 0.05)

Adverse Events: There were no episodes of hypotension and no return visits within 1 week of discharge

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Due to the small sample size (n=38) the confidence interval for the primary outcome (10, 63%) is very wide (imprecise).

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	There are some similarities between the study patient population and our patient population at NYU. Our ED sees a significant number of severe asthmatics of variable ages. Our patients, however, are not kept in the ED for the duration of their exacerbation management and are often either discharged home when clinically improved or admitted to the inpatient service within hours of their arrival to the ED. Patient demographics in the study are also similar to our patient population, however, a number of our patients would be considered obese. Our initial management of acute asthma exacerbations would also differ in that we would use Nebulized Ipatropium Bromide (which was unavailable in this study) and would use a higher initial dose of Dexamethasone (0.6 mg/kg, Max 16 mg) than was used in the study population (0.2 mg/kg, no max provided).
Were all clinically important outcomes considered?	Yes. The investigators considered length of ED stay, improvement in respiratory status (both PEFR and Asthma Score), subsequent ED visits, and adverse events in their study. The study would have benefited from a description of how adverse events were assessed.
Are the likely treatment benefits worth the potential harm and costs?	This study demonstrated that using a high dose Magnesium infusion in severe asthma exacerbations in the pediatric emergency room led to earlier discharge times than using only intravenous $MgSO_4$ bolus therapy. This ultimately led to reduced hospital admission, ED length of stay, and overall cost. NNT: 1/ARD = 1/0.365 = 2.7. You would need to treat 2.7 patients with HDMI to discharge 1 additional patient compared to standard bolus dosing at or before 24 hours.

CLINICAL BOTTOM LINE

BACKGROUND: Asthma exacerbation among children is one of the most common reasons for pediatric emergency department visits. While traditional interventions including bronchodilators, corticosteroids, and a single dose of IV Magnesium have proven to be effective in the management of acute non-infectious asthma, no prior study had examined the effectiveness of a continuous infusion Magnesium. At high unbound levels, Magnesium acts to relax smooth muscle, ultimately leading to bronchodilation. This study was a prospective randomized control trial in a single Pediatric ED (Paraguay).

CLINICAL QUESTION: In pediatric patients with severe asthma not responsive to conventional therapy in the Emergency department, does a high dose infusion of Magnesium sulfate when compared to standard dose bolus of Magnesium sulfate result in fewer admissions?

DESIGN/VALIDITY: The study was an open label study of 38 patients. Neither the patient, nor the treating physician, were blinded to the treatment. The physician at time of discharge was, however, blinded to the treatment the patient had received (IV Magnesium bolus vs. IV Magnesium infusion). The study attempted to use objective measures of asthma severity (Global Initiative Asthma Score, Woods-Downes Asthma Score) to reduce subjective individual assessment of asthma severity. Even using this, however, the study would have also had some degree of subjectivity in that the Asthma Score used to determine severity of exacerbation and response to treatment was dependent on Peak Expiratory Flow Rates, which are subjective and dependent on patient effort (the article also states that peak flow meters are not readily available in this country and thus few patients would have used them before).

The primary concern with this study is the small number of patients. This study was a small study and only 38 patients were included in the study analysis (the authors specifically state they had a difficult time with enrollment due to their exclusion criteria of recent antibiotic use and the ease of availability of antibiotics in Paraguay). The study was also stopped early possibly inflating the risk difference seen particularly with such a small sample size. Furthermore, the study did not use a assess inter-rater reliability of the study assessments. The study would have benefited from a description of how the adverse outcomes were assessed and a comparison of the co-interventions received in the study groups.

PRIMARY RESULTS: The absolute risk in those patients treated with high-dose Magnesium sulfate infusion was 47% (i.e. 47% of patients who received HDMI were discharged home from the ED within 24 hours post treatment) in comparison with the absolute risk of patients in the single IV Magnesium bolus group, which 10.5%. The absolute risk difference between the high dose Magnesium infusion group and the Magnesium bolus group was 36.5%, 95% CI (10, 63%) suggesting that patients in the HDMI group were 36.5% more likely to be discharged home at 24 hours compared with the $MgSO_4$ bolus group. This is statistically significant difference of benefit of the high dose infusion group.

APPLICABILITY: Applying this studies results may be problematic for a number of reasons. They excluded a large number of patients with fever and their admission criteria are significantly different from ours. Patients stayed in the ED until they are fit for discharge or admitted to the ICU. The ED length of stay in the study was averaged 41 hours. In our patient population, asthma exacerbation is a common reason for presentation to the Pediatric ED. In our ED, however, we typically do not manage patients for the entire duration of their exacerbation and normally admit to the inpatient service or discharge home within a few hours of their initial presentation.

Our initial management of acute asthma exacerbations would also differ in that we would use nebulized Ipatropium Bromide (which was unavailable in this study) and would use a higher initial dose of Dexamethasone (0.6 mg/kg, Max 16mg) than was used in the study population (0.2 mg/kg, no maximum provided).

AUTHOR'S CONCLUSIONS: "In this small study, the utilization of HDMI (50 mg/kg/hour/4 hours) as adjunctive therapy for noninfectious–mediated asthma expedites discharges from the ED."

POTENTIAL IMPACT: While high dose continuous Magnesium infusion is not currently used in our ED practice, it may provide an additional option to consider for the management of severe asthmatics whose exacerbation is severe enough to warrant hospital admission after standard therapies have failed (i.e. bronchodilators, steroids). Furthermore, high dose Magnesium sulfate infusion may provide an alternative option to the other asthma medications currently used for severe disease such as Aminophylline, Terbutaline, and Ketamine that have greater safety concerns.

ASTHMA EXACERBATION: NEBULZED IPATROPIUM

In children presenting to the emergency department with an acute asthma exacerbation, does the addition of nebulized Ipatropium to 3 doses of nebulized Albuterol and a single dose of oral Prednisone or Prednisolone when compared to nebulized Albuterol and oral Prednisone or Prednisolone alone, reduce the time to discharge, the number of nebulizer treatments before discharge, and the rate of hospitalization?

Michael Mojica, M.D.
June 2017

Zorc JJ, Pusic MV, Ogborn CJ, Lebet R, Duggan AK

IPRATROPIUM BROMIDE ADDED TO ASTHMA TREATMENT IN THE PEDIATRIC EMERGENCY DEPARTMENT

Pediatrics. 1999 Apr;103(4 Pt 1):748-52.
PubMed ID: 10103297

STUDY DEFINITIONS	
POPULATION	Inclusion: > 12 months of age, presenting to the ED with wheezing, eligible for treatment on a Critical Pathway Exclusion: Signs of respiratory failure, required initial therapy in addition to the Critical Pathway (e.g. continuous Albuterol, or subcutaneous Epinephrine or terbutaline), pretreatment with corticosteroids (within 3 days) or Ipratropium (within 24 hours), history of glaucoma, cystic fibrosis, or sickle cell disease. Setting: Single Pediatric Hospital Emergency Department, 7/1997-7/1998
INTERVENTION	1 ml nebulized Ipatropium (250 mcg/ml) with each dose of nebulized Albuterol
CONTROL	1 ml nebulized Normal Saline (Placebo) with each dose of nebulized Albuterol
CO-INTERVENTIONS	1. 3 doses of nebulized Albuterol every 20 minutes: 2.5 mg/3 ml if < 30 kg or 5.0 mg/6 mL if ≥ 30 kg) via face mask with oxygen at 5-6 liters/minute 2. 1 dose of oral Prednisone or Prednisolone (2 mg/kg, maximum of 80 mg) Patients who vomited or unable to take oral medications given parenteral methylprednisolone at the discretion of the treating physician. Baseline assessment of asthma severity score (See Appendix). Classified as Mild (1–3), Moderate (4–6) or Severe (7–9). Interrater reliability (kappa 0.6) Further treatments after 1 hour at the discretion of the treating physicians Physicians asked not to administer Ipratropium outside of the study unless a patient was clinically worsening and a decision to admit had been made.
OUTCOME	Primary Outcome: Disposition: Discharge home, admission to ward, admit to intensive care unit Secondary Outcomes: Discharged Patients: 1. Number of Albuterol nebulizers before discharge. 2. Time to discharge: Time of 1st aerosol to the time of discharge instructions. 3. Return visits to the same ED within 72 hours (via administrative logs) 4. Hospital charges: Separate from physician charges, based on severity level with additional charge per hour for observation beyond the initial 2 hours.
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Study vials were block randomized in groups of eight in the investigational pharmacy.
Was randomization concealed?	Yes. Study vials containing either normal saline (Placebo) or Ipatropium were prepared by the investigational pharmacy. Both solutions were clear, odorless, and indistinguishable in the liquid and nebulized forms.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. See Table 2. Patients were similar with regard to age, gender, proportion, ethnicity, previous asthma admissions, respiratory rate, oxygen saturation and asthma severity score.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study was described a “double blinded” though Investigators, physicians, nurses, and patients were all blinded.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. The majority of the outcomes were measured prior to ED discharge. The exception is return visits which were determined from an administrative database. Other methods to follow up discharged patients was not presented.
Were patients analyzed in the groups to which they were randomized?	Yes. An intention to treat analysis was performed involving 427 patients. 11 (2.6%) patients were treated with Ipatropium outside of the study protocol. A per protocol analysis was not presented though the authors state that results did not differ when patient with protocol violations were excluded (data not presented).
Was the trial stopped early?	Yes. The trial was stopped early. An interim analysis revealed that a larger sample size (1,600 rather than the initially calculated 900 patients) would be needed for the primary outcome of discharge. This was not feasible and enrollment was discontinued after 1 year. Adequate power was present to determine clinically significant reductions in the outcomes of time to discharge (30 minutes) and number of albuterol doses (0.3).

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 427 (Ipatropium: 211, Placebo 216)

Admission
Ipatropium: 18% (38/211)
Placebo: 22% (48/216)
Risk Difference: 4.2%, 95% CI (-3.4, 11.8%),
No difference in the subgroup analysis based on severity.
When moderate and severe subgroups were combined the risk difference increased to 8% but was still not statistically significant.

Mean Time to Discharge
Ipatropium: 185 ± 69 minutes
Placebo: 213 ± 82 minutes
Mean Difference: 28 minutes, p = 0.001
In the severity subgroup analysis, there was a statistically significant difference in the mild and moderate subgroups but not in the severe subgroup.

Median Number of Albuterol Nebulizer Treatments
Ipatropium: 3 doses
Placebo: 4 doses
Median Difference: 1 dose, p < 0.01
In the severity subgroup analysis, there was a statistically significant difference in the mild and severe subgroups but not in the moderate subgroup.

Return Visits
Ipatropium 4%
Placebo 2%, p = 0.38

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The confidence intervals for the differences were not provided. The confidence interval for the admission absolute risk difference was calculated by the reviewer and is fairly wide.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Yes. The setting was a single, urban Children's Hospital emergency department. The patient characteristics provided are similar with the exception of much higher proportion of African American patients.
Were all patient important outcomes considered?	The outcome of disposition is always somewhat subjective. It would have been helpful to determine if patients met predefined discharge criteria. Importantly, no predefined safety outcomes were presented. Change in the asthma severity score at the time of disposition decision was not reported.
Are the likely treatment benefits worth the potential harm and costs?	The financial cost of Ipatropium is insignificant compared to the its efficacy. In the study population, a $36 per patient (1999) reduction in costs was associated with Ipatropium use. No safety outcomes were presented.

CLINICAL BOTTOM LINE

BACKGROUND: The efficacy of intermittent or continuous inhaled beta agonists and oral or intravenous corticosteroids has been well established in the treatment of status asthmaticus. A variety of agents, such as Magnesium, Ketamine and Intravenous beta agonists have been suggested as useful adjuncts in the pediatric patients unresponsive to this standard therapy. Ipatropium Ipratropium bromide is a synthetic derivative of atropine with anticholinergic properties. It was designed to act locally in the lung with minimal systemic absorption. Ipatropium has demonstrated efficacy is small trails without significant safety concerns

CLINICAL QUESTION: In children with an acute asthma exacerbation in the emergency department, does the addition of nebulized Ipatropium to nebulized Albuterol and oral Prednisone or Prednisolone when compared to nebulized Albuterol and oral Prednisone or Prednisolone alone reduce the time to discharge, the number of nebulizer treatments before discharge, and the rate of hospitalization?

DESIGN/VALIDITY: The was a well-designed, placebo controlled, blinded trail of 3 doses of nebulized Ipratropium compared to placebo added to nebulized Albuterol and a single oral corticosteroid dose. Treatment groups were similar with regard to potential confounding variables. The primary intention to treat analysis included 427 patients (Ipatropium 211, Placebo 168). A subgroup analysis of the outcomes based on exacerbation severity was also presented.

There are a few minor validity concerns. The inclusion of multiple visits by the same patient (427 visits made by 365 individuals) violates the assumptions of randomization. However, the results of the study did not differ when patients with repeat visits were excluded (data not presented).

Follow-up data on discharged patients was obtained via an administrative database and attempts to contact patients were not conducted. Importantly, no predefined safety outcomes were presented.

The trial was stopped early after the assumptions on which the initial sample size determination was based were found to be inaccurate and enrollment of a significant higher number of patients was not deemed feasible. However, the trial had adequate power to detect a clinically significant difference in the outcomes of time to discharge and the number of Albuterol doses per subject.

PRIMARY RESULTS: There was no statistically significant difference in the rate of admission between the 2 study groups (Ipatropium: 18%, Placebo: 22%, Absolute Risk Difference: 4%, 95% CI (-3.4, 11.8%). There was also no difference in the subgroup analysis based on severity. When moderate and severe subgroups were combined the absolute risk difference increased to 8% but the difference was not statistically significant. Some may consider an 8% decrease in admission to be a clinical significant difference. The 95% confidence interval was for this difference was not provided.

The mean time to discharge was significantly lower in the Ipatropium group (185 ± 69 minutes) then the Placebo group (213 ± 82 minutes) (Mean Difference: 28 minutes, p = 0.001). The authors defined a reduction of 30 minutes as a clinically significant difference in their sample size determination. In the severity subgroup analysis, there was a statistically significant difference in the mean time to discharge for Ipatropium in the mild and moderate subgroups but not in the severe subgroup.

The median number of Albuterol nebulizer treatments was significantly lower in the Ipatropium group (3 doses) then in the Placebo group (4 doses) (Median Difference: 1 dose, $p < 0.01$). The clinical significant of a single dose of Albuterol other than reducing ED length of stay is unclear.
The authors defined a reduction in the number of Albuterol doses of 0.3 doses as a clinically significant difference in their sample size determination. In the severity subgroup analysis, there was a statistically significant difference in the median number of Albuterol treatments favoring Ipatropium in the mild and severe subgroups but not in the moderate subgroup.

APPLICABILITY: The study was conducted in a single urban pediatric emergency department and it is likely that the study's results are applicable to that setting. The inclusion of patients with mild, moderate and severe exacerbation enhances its generalizability. Prior Ipatropium studies focused primarily on severe exacerbations.

AUTHOR'S CONCLUSION: "Overall, our study demonstrated a benefit of adding ipratropium to ED treatment for childhood asthma. Time to discharge and number of nebulizer treatments were reduced in the overall study group, and benefits were identified in all severity subgroups including the mildest subgroup. Future research is needed to reproduce these results in other settings, measure the effect of ipratropium on asthma hospitalizations, and assess the cost-effectiveness of the medication."

POTENTIAL IMPACT: The benefit of reviewing a study 18 years after its publication is that the study's impact has already been determined. This and other studies demonstrated the efficacy of Ipatropium added to standard treatment of inhaled beta agonists and oral corticosteroids. Most current clinical pathways include the use of Ipatropium for moderate to severe exacerbations. The benefit of Ipatropium for mild asthma exacerbations is less well established.

APPENDIX: BASELINE CLINICAL ASTHMA SCORE

CLINICAL ASTHMA SCORE*			
SCORE	ACCESSORY MUSCLE SCORE	WHEEZE SCORE	DYSPNEA SCORE
0	No retractions	No wheezes and well	Absent dyspnea
1	Intercostal retraction	End expiratory wheezes	Normal activity & speech Minimal dyspnea
2	Intercostal and suprasternal retraction	Pan-expiratory ± inspiratory wheezes	Decreased activity, 5-8 word sentence, Moderate dyspnea
3	Nasal Flaring	Wheeze audible without stethoscope	Concentrates on breathing < 5 word sentence Severe dyspnea

*Shuh, J Pediatrics 1995, PubMed ID: 7699549

ASTHMA EXACERBATION: KETAMINE

In children (2-18 years) with a moderately severe asthma exacerbation can an intravenous bolus of Ketamine (0.2 mg/kg) followed by a continuous 2-hour infusion (0.5 mg/kg/hour) added to standard therapy when compared to Placebo improve symptoms as measured by a validated asthma score?

Karen Franco M.D., Jeffery Fine, M.D.

August 2005

Allen JY, Macias CG.

THE EFFICACY OF KETAMINE IN PEDIATRIC EMERGENCY DEPARTMENT PATIENTS WHO PRESENT WITH ACUTE SEVERE ASTHMA

Ann Emerg Med. 2005 Jul;46(1):43-50.
PubMed ID: 15988425

STUDY DEFINITIONS	
POPULATION	Inclusion: 2 to 18 years, pulmonary index score 8-12 (moderate to severe) after 3 treatments with Albuterol/Ipatropium. Exclusion: Temperature > 39 C (102 F), focal infiltrate on chest radiograph, use of oral, parenteral, or inhaled glucocorticoids within the previous 72 hours, history prematurity, bronchopulmonary dysplasia, coexisting primary parenchymal pulmonary disease (e.g. cystic fibrosis), coexisting congenital heart diseases, hypertension, psychotic disorders, pregnancy, allergy to Ketamine Setting: Single Children's Hospital ED, 11/2002-3/2004
INTERVENTION	Ketamine 0.2 mg/kg bolus intravenously over 1 to 2 minutes, followed by continuous infusion of 0.5 mg/kg/hour for 2 hours
CONTROL	Equivalent volume of normal-saline Placebo
CO-INTERVENTIONS	Institution reactive airways disease protocol: 1. Up to 3 treatments with nebulized Albuterol (2.5 mg/dose, with up to 3 nebulized treatments of Ipratropium bromide 500 mcg/dose) (Alternatively, an equivalent 6-puff dose of Albuterol (90 mg/ puff) by a metered-dose inhaler with a spacer with an equivalent 2-puff dose (18 mg/dose) of Ipratropium bromide may be used in the same protocol). 2. 2 mg/kg dose of PO prednisone or IV methylprednisolone (max 80 mg). No Ipratropium, Magnesium or Terbutaline during 2-hour infusion. 3. After infusion, clinical management at the discretion of attending physician.
OUTCOME	Primary Outcome: Reduction in Pulmonary Index Score (see Appendix) Secondary Outcomes: Disposition (discharge, ward, intermediate care, ICU) 48-hour follow-up: Symptom questionnaire, unscheduled return visit
DESIGN	Interventional: Randomized clinical trial.

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes, A randomization list was generated by coin flip in the pharmacy. This was a convenience sample (7am-11pm) which may introduce selection bias.
Was randomization concealed?	Unclear. Allocation concealment was not specifically stated but it appears that randomization and allocation were performed by the pharmacy so that there was not an opportunity to bias the allocation process.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. (Table 2 & 3) There was no significant difference between Ketamine or Placebo groups in demographic data, prior asthma severity, severity of exacerbation (symptoms, pulmonary index score), prior hospital/ICU admissions, ED visits or family history of asthma.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Patients receiving Ketamine may have experienced some side effects in contrast to the placebo group, but there is nothing to suggest that it may have affected the outcomes. The assessing physician correctly identified the study group approximately 2/3 of the time indicating that he may not have been fully blinded.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. The primary outcome was change in the Pulmonary Index Score at 2 hours. All patients remained in the emergency department for the 2 hours of the infusion. In the Ketamine group 72.7% (24/33) were available for 48-hour phone follow up. In the Placebo group 82.9% (29/35) were available for 48-hour phone follow up.
Were patients analyzed in the groups to which they were randomized?	Yes. (Figure 1). 87.8% (29/33) completed the Ketamine infusion. 94.3% (33/35) completed the Placebo infusion. Patients who terminated study prior to completion were included in analysis in the group they were assigned to using their last Pulmonary Index score. There was no difference in the primary analysis if these patients were included in the analysis or not.
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 68 (Ketamine n = 33, Placebo n = 35)

Mean Decrease in Pulmonary Index Score at 2 hours
Ketamine: 3.6 +/- 1.3
Placebo: 3.2 +/- 2.0
Risk Difference 0.4, 95% CI (-0.4, 1.3).
The authors considered a clinically significant decrease in pulmonary index score to be 2 points in their sample size determination.

There was no significant difference in pulmonary index score between the Ketamine and Placebo group at 0, 30, 60, 90 and 120 minutes (Figure 2).

Secondary Outcomes:
No statistically significant difference in: disposition, behavioral changes, return visits

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See confidence interval for risk difference above. The confidence interval is wide (imprecise) due to the study's small sample size. However, the confidence interval does not include the 2-point difference in the pulmonary index score that the authors considered clinically significant.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Yes. Patients were children with asthma experiencing a moderately severe asthma exacerbation presenting to an ED setting.
Were all patient important outcomes considered?	Yes. The pulmonary index score is a composite outcome measure including many of the characteristics use to assess asthma severity.
Are the likely treatment benefits worth the potential harm and costs?	There was no treatment benefit, and no adverse events reported. Therefore, no assessment about potential harm or costs can be made.

CLINICAL BOTTOM LINE

BACKGROUND: Ketamine has both direct and indirect bronchodilation effects and may be a useful adjunct to standard therapy in those with severe asthma. There are a few published case reports looking at varying doses of Ketamine in acute asthma exacerbations in children which have found some improvement in symptoms. There are however no clinical trials addressing the utility of Ketamine in the pediatric population.

CLINICAL QUESTION: In children (2- 18 years) with a moderately severe asthma exacerbation can an intravenous bolus of Ketamine (0.2 mg/kg) followed by a continuous 2-hour infusion (0.5 mg/kg/hour) added to standard therapy when compared to Placebo improve symptoms as measured by a validated asthma score?

DESIGN/VALIDITY: This was a very well-designed randomized clinical trial that included 68 patients in the primary analysis. Patients with a moderate to severe asthma exacerbation were randomized to receive an intravenous bolus of Ketamine (0.2 m/kg) followed by a continuous 2-hour infusion (0.5 mg/kg/hour) or an equivalent volume of Placebo. It is often difficult to assess the contribution of a single intervention when multiple interventions are provided simultaneously. The primary validity concern is the small sample size.

PRIMARY RESULTS: No benefit was seen at the dose of Ketamine used in this study. The mean decrease in the pulmonary index score at 2 hours in the Ketamine group was 3.6 +/- 1.3 and in Placebo group was 3.2 +/- 2.0. The decrease in Pulmonary index score was neither clinically significant (≥ 2 points) nor statistically significant (Risk Difference 0.4, 95% CI (-0.4, 1.3)). There was no statistically significant difference in the secondary outcomes of disposition, behavioral changes and return visits.

APPLICABILITY: The primary outcome is a decrease in the pulmonary index score. Because elements of the score are subjective it would have been helpful to have a measurement of inter-rater reliability.

AUTHOR'S CONCLUSION: "We conclude that ketamine given at 0.2 mg/kg, followed by an infusion of 0.5 mg/kg per hour for 2 hours, provided no incremental benefit to standard therapy in this cohort of children with a moderately severe asthma exacerbation."

POTENTIAL IMPACT: The results from this study do not support the use of Ketamine as an adjunct to standard therapy in moderately severe asthma exacerbations in children. The small sample size should be considered when interpreting the study's results. In is unclear if larger doses of Ketamine may show a benefit but since Ketamine is a sedative, the risk of potential side effects at higher doses must be weighed against the possible benefits.

PULMONARY INDEX SCORE

	Respiratory Rate					
Score	< 6 years	> 6 years	Wheezing	I:E Ratio	Accessory Muscle Use	Oxygen Saturation
0	< 30	< 20	None	2:1	None	99-100%
1	31-45	21-35	End expiration	1:1	+	96-98%
2	46-60	36-50	Entire expiration	1:2	++	93-95%
3	> 60	> 50	Entire breath (none)	1:3	+++	< 93%

ASTHMA EXACERBATION: MAGNESIUM (META-ANALYSIS)

In children with a moderate to severe asthma exacerbation in the emergency department does intravenous Magnesium Sulfate with inhaled beta-agonists and corticosteroids compared to inhaled beta-agonists and corticosteroids alone reduce the hospitalization rate?

Louis Spina, M.D., Michael Mojica, M.D.
June 2008

Cheuk DK, Chau TC, Lee SL.

A META-ANALYSIS ON INTRAVENOUS MAGNESIUM SULPHATE FOR TREATING ACUTE ASTHMA

Arch Dis Child. 2005 Jan;90(1):74-7.
PubMed ID: 15613519

STUDY DEFINITIONS	
POPULATION	Inclusion: Controlled clinical trials, < 18 years, acute, moderate to severe asthma exacerbation, intravenous Magnesium sulfate at any dose, outcome measures of hospitalization, ICU admission, clinical symptom scores, or pulmonary function tests, published and unpublished studies, no language restriction. Exclusion: Multiple publications of same data Setting: 5 Emergency Departments, Studies published 1996-2000
INTERVENTION	Intravenous Magnesium at any dose
CONTROL	Placebo
CO-INTERVENTIONS	Inhaled beta two agonists and systemic steroids
OUTCOME	Primary Outcome: 1. Rate of hospitalization Secondary Outcomes: 1. Rate of persistent severe bronchoconstriction (PEFR < 60% predicted) 2. Group differences in symptom scores 3. Percentage change in pulmonary function tests
DESIGN	Systematic Review and Meta-analysis of randomized clinical trials

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review explicitly address a sensible clinical question?	Yes. The authors sought to determine if intravenous Magnesium Sulfate is effective in preventing hospitalization in children with acute asthma exacerbations when used in conjunction with standard therapies. They also analyzed measures of pulmonary function as secondary outcomes.
Was the search for relevant studies detailed and exhaustive?	Yes. The authors searched Medline, PubMed, Embase, Cochrane (Library & Central Register of Controlled Trials) and China Journal Net. They also hand searched reference lists and contacted authors and specialists in the field for unpublished data. A funnel plot of precision by effect size was not suggestive of publication bias though its interpretation is limited by only 5 data points. A Begg's test for publication bias was not reported.
Was the risk of bias of the primary studies assessed?	Yes. All five studies had Jadad scores ≥ 4 (out of five).
Were the selection and assessment of studies reproducible?	Unclear. The authors state that all assessments were done by 2 independent reviewers and disagreements were resolved by consensus. However, they did not report if interrater reliability was assessed for either study quality or inclusion.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

Yes. In the Forest Plot for hospitalization (Figure 1) the confidence intervals overlap and favor treatment. The Cochrane Q Test for hospitalization (Q = 0.13) and persistent PEFR < 60% predicted (Q = 0.97) indicate no significant heterogeneity of results. The results were heterogeneous for percentage improvement in PEFR (Q < 0.001) and clinical symptoms score (Q = 0.001) at study end. I^2 statistics to assess the a quantitate measure of heterogeneity were not presented.

WHAT ARE THE OVERALL RESULTS OF THE REVIEW?

N = 182 (number in each study group not presented)

Primary Outcome: Admission
Absolute risk of admission in each study group was not presented.
Risk Reduction: 25.7%, 95% CI (12.4, 38.9%)
Odds Ratio: 0.29, 95% CI (0.14, 0.59)

Secondary Outcomes
Persistent PEFR < 60% predicted:
Odds Ratio: 0.155, 95% CI (0.057, 0.422)

Percentage improvement in PEFR at study end:
Risk Difference: 8.58%, 95% CI (0.94, 16.22%)

Clinical symptoms score at study end:
Risk Difference: 1.33, 95% CI (0.31, 2.36)

Odds Ratio = Ketamine/Placebo
Risk Difference = Ketamine - Placebo

DID THE REVIEW ADDRESS CONFIDENCE IN EFFECT ESTIMATES?

See confidence intervals above. The authors did not specify what they thought to be a clinically significant difference in the primary outcome.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were all patient-important outcomes considered?	No. Indications for hospitalization are subjective. Criteria for hospitalization can vary from hospital to hospital and physician to physician. Also, there were different clinical scores and methods in the different studies. No mention was made of follow-up (to assess rebound/relapse of the asthma episode) nor were events such as intubation or assisted ventilation reported.
Are any postulated subgroup effects credible?	A sensitivity analysis was planned excluding studies with poor quality (Jadad score < 3) but all studies had an Jadad score of 4 or above. Planned subgroup analysis were not conducted because stratification of study data was not available.
What is the overall quality of the evidence?	Individual study quality was good (Jadad Score ≥ 4). However, the meta-analysis included only 182 patients. It also included studies using different Magnesium dosages.
Are the benefits worth the costs and potential risks?	Possibly. Intravenous Magnesium sulfate is inexpensive and is relatively safe. The number needed to treat is small (NNT = 1/ARD = 1/0.257 = 4). 4 patients with a moderate to severe asthma exacerbation would need to be treated with Magnesium to prevent one additional hospitalization compared to treatment without magnesium.

CLINICAL BOTTOM LINE

BACKGROUND: The exact mechanism of action of Magnesium in asthma is unclear. Proposed mechanisms include: a decrease in calcium uptake in bronchial smooth muscle leading to bronchodilation, inhibition of mast cell degranulation leading to a decrease in inflammatory mediators and a decrease in acetylcholine release leading to a decreased in smooth muscle excitability. A 2003 Cochrane meta-analysis of 7 trials (5 adult, 2 pediatrics) concluded that current evidence did not support routine use of intravenous Magnesium sulfate in all patients with acute asthma presenting to the emergency department. Multiple small randomized clinical trials of the efficacy of Magnesium have been conducted in pediatrics but the results have varied. A meta-analysis of these trials would could assist in determining Magnesium's efficacy.

CLINICAL QUESTION: In children with a moderate to severe asthma exacerbation in the emergency department does intravenous Magnesium sulfate with inhaled beta-agonists and steroids compared to inhaled beta-agonists and steroids alone reduce the hospitalization rate?

DESIGN/RISK OF BIAS: This is a well-designed meta-analysis of 5 pediatric studies on intravenous Magnesium including 182 patients. The included studies were heterogeneous with respect to inclusion criteria, baseline characteristics, Magnesium dosing, co-therapies and outcomes assessed. Study inclusion and quality were assessed by two investigators and disagreements were resolved by consensus. However, no measure of inter-rater reliability was reported.

PRIMARY RESULTS: For the primary outcome, the intravenous magnesium group was statistically significantly less likely to be admitted (absolute risk reduction: 25.7%, 95% CI (12.4, 38.9%). The Number needed to treat is low (1/ARD = 1/0.257 = 4, 95% CI (3, 8)). 4 patients with a moderate to severe asthma exacerbation would need to be treated with magnesium to prevent one additional hospitalization to compared to treatment without magnesium.

Statistically significant improvement was also seen in the secondary outcomes of: odds ratio of persistent peak expiratory flow rate (PEFR) < 60% predicted (0.155, 95% CI (0.057, 0.422)), difference in percentage improvement of PEFR at study end (8.58%, 95% CI (0.94, 16.22%))
and difference in clinical symptom score at study end (1.33, 95% CI (0.31, 2.36)).

APPLICABILITY: The study's results are likely generalizable to children with a moderate to severe asthma exacerbation presenting to the emergency department who do not respond adequately to beta agonists and corticosteroids. The optimal dosing regimen cannot be determined from the study. 25 mg/kg was used in 2 studies, 40 mg/kg was used in 2 studies and 75 mg/kg was used in 1 study. A dose-response relationship was not reported.

AUTHOR'S CONCLUSION: "Based on existing data, intravenous magnesium sulphate is likely to be effective in avoiding hospitalisation and improving bronchoconstriction and clinical symptoms of moderate to severe acute asthma in children, when added to standard therapies of inhaled bronchodilators and systemic steroids.

Further studies are needed to evaluate the effectiveness of intravenous magnesium sulphate in different severity classes of asthma and in patients of different age groups. Studies should also aim at further defining the indications, possible contraindications, and optimal dosage of intravenous magnesium sulphate."

POTENTIAL IMPACT: Although the authors demonstrate that intravenous Magnesium Sulfate may decrease hospitalization rate in moderate to severe asthmatic children who present to the emergency department the authors conclusions are limited by the variety of magnesium dosages used and the use of a someone subjective primary outcome of hospitalization without reporting on clinical follow up. Optimum dosing and specific indications based of disease severity need to be studied to further determine the risks and benefits of intravenous Magnesium.

ASTHMA EXACERBATION: METERED DOSE INHALERS

In children 12-60 months of age with a history of recurrent wheezing who present to the emergency department with wheezing is Albuterol delivered by a Metered Dose Inhaler with an Asthma Spacer Device equivalent to Albuterol delivered by a Nebulizer in generating clinical improvement as measured by the change in the pulmonary index score over 1 hour?

Michael Mojica, M.D.
July 2017

Ploin D, Chapuis FR, Stamm D, Robert J, David L, Chatelain PG, Dutau G, Floret D.

HIGH-DOSE ALBUTEROL BY METERED DOSE INHALER PLUS A SPACER DEVICE VERSUS NEBULIZATION IN PRESCHOOL CHILDREN WITH RECURRENT WHEEZING: A DOUBLE-BLIND, RANDOMIZED EQUIVALENCE TRIAL

Pediatrics. 2000 Aug;106(2 Pt 1):311-7.
PubMed ID: 10920157

STUDY DEFINITIONS	
POPULATION	Inclusion: 12-60-month-old, acute wheezing, ≥ 1 episode of prior wheezing Exclusion: 1. Oxygen saturation < 90% 2. Inhaled or systemic corticosteroids within 24 hours 3. Chronic disease: respiratory, cardiac, renal or liver insufficiency, immunodeficiency, encephalopathy 4. Height and weight > 2 standard deviations below the standard for age. Setting: 2 Adjacent Pediatric ED's (France), 12/1995-3/1997.
INTERVENTIONS	Albuterol Nebulizer: 0.15 mg/kg (0.03 ml/kg). Minimum dose 0.3 ml. Diluted in isotonic saline to a volume of 4 ml. Air flow set at 8 liters/min. Albuterol Metered Dose Inhaler with an Asthma Spacer Device: 1 puff/2 kg (50 mcg/kg). Maximum 10 puffs. Each puff was followed by 8 breaths.
CONTROLS	Placebo Nebulizer: 0.03 ml/kg. Minimum dose 0.3 ml. Diluted in isotonic saline to a volume of 4 ml. Air flow set at 8 l/min. Placebo Metered Dose Inhaler with an Asthma Spacer Device: 1 puff/2 kg. Maximum 10 puffs. Each puff was followed by 8 breaths.
CO-INTERVENTIONS	Treatment lasted 10 minutes (8-9 minutes nebulization, 1-2 minutes MDI ASD) Followed by a 10-minute rest period before assessments Assessments: Time 0, 20, 40 and 60 minutes, Oxygen saturation, respiratory rate, heart rate. I:E ratio (by impedance), Pulmonary index score (Appendix) Treatments given 3 times at Q20-minute intervals (Time 0, 20, 40 minutes) Total study duration of 60 minutes. Febrile children treated with Acetaminophen or Aspirin
OUTCOME	Primary Outcome: Change in pulmonary index (See Appendix) from prior to 1st treatment (Time 0 min) and the end of the 3rd treatment (Time 60 min). Secondary Outcomes: 1. Improvement in the pulmonary index score after each of the 3 treatments (Mild: 0-6, Moderate: 7-9, Severe (10-12) 2. Admission to the hospital, indication for admission 3. Parents assessment of devices 1. Ease to use and 2. Acceptance by child 4. Improvement in Sao_2 (From Time 0 min to Time 60 min).
DESIGN	Interventional: Randomized clinical trial (Equivalence hypothesis)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Randomization was performed in blocks of 4. Patients Allocated by 1. Delivery device and 2. Order of use into 4 treatment groups. Each group received an active treatment 1. Albuterol via MDI-ASD then Placebo Nebulizer 2. Placebo via MDI-ASD then Albuterol Nebulizer 3. Albuterol Nebulizer then Placebo MDI-ASD 4. Placebo Nebulizer then Albuterol via MDI-ASD
Was randomization concealed?	Yes. The Placebo and Albuterol vials and the MDI packages were identical and were prepared by the pharmacy. Though not explicitly stated, there does not appear to be an opportunity to bias the randomization process.
Were patients in the study groups similar with respect to known prognostic factors?	No. See Table 2. There was a statistically significant difference in the initial oxygen saturation of 1.3% though this difference is likely not of clinically significance. While there was no statistically significant difference in initial severity, in the MDI group 91% of the patients were classified as moderate or severe and in the Nebulizer group 78% of the patients were classified as moderate or severe. In addition, there was a 2-point difference in the baseline pre-treatment pulmonary index score. Other authors have considered a 2-point difference to be clinically significant.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Investigators, patients, and parents were unaware of the group assignments.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Study measurements ended at 60 minutes which was 10 minutes after the completion of the 3rd treatment. The authors state that no patients required repeat ED visits but did not state how this was assessed and whether all patients were assessed.
Were patients analyzed in the groups to which they were randomized?	Yes. See Figure 3. 32 patients were randomized to the MDI-ASD group. 31 were included in the intention to treat analysis and 30 in the per protocol analysis. 32 patients were randomized to the Nebulizer group. 32 were included in the intention to treat analysis and 30 in the per protocol analysis.
Was the trial stopped early?	No. The trial was not stopped early.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 63, MDI-ASD: 31, Nebulizer: 32 (Intention to treat)

Change in Pulmonary Index Score (0-60 minutes)
90% confidence interval was -1 to +1 points. The authors defined equivalence as a 90% confidence interval with the range of -1.5 and +1.5 points.

Change in Pulmonary Index Score after each Treatment
Mean change from baseline to time measured
20 minutes: MDI-ASD: - 3 points, Neb: - 3 points, Δ 0
40 minutes: MDI-ASD: - 4 points, Neb: - 4 points, Δ 0
60 minutes: MDI-ASD: - 6 points, Neb: - 5 points, Δ -1
There was statistically significant improvement in both groups

Admission (for treatment failure)
MDI-ASD: 6.5% (2/31)
Nebulizer: 6.3% (2/32)

PARENT DEVICE SATISFACTION

	METERED DOSE INHALER	NEBULIZER	NO PREFERENCE
Easier to Use	95%	5%	1%
Better child acceptance	62%	27%	11%

Change in Oxygen Saturation (0-60 minutes)
90% confidence interval for the mean difference: -0.57, 1.63%. Mean difference not presented. Not clinically significant.

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence intervals are only provided for the primary outcome of change in pulmonary index score and change in oxygen saturation from 0-60 minutes. The two study groups were equivalent by the authors definition of a 90% confidence interval within the range of -1.5 and +1.5 points for the primary outcome.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Likely yes. Demographic data is presented in Table 2. Unclear if the French population differs from ours. The treatment regimen differed somewhat from ours. Corticosteroids were not given and nebulizers were driven by air flow and not oxygen.
Were all patient important outcomes considered?	Yes. Both clinical parameters typically used to assess asthma and parent oriented outcomes were included.
Are the likely treatment benefits worth the potential harm and costs?	The benefit of utilizing an MDI with an ASD in the emergency department is that parents can be taught the correct uses of the devices and then be discharged with the devices that they used eliminating the need to fill prescriptions. A cost benefit analysis was not included.

CLINICAL BOTTOM LINE

BACKGROUND: Metered dose inhalers (MDI) are difficult for young children to use. They require coordinating inhalation with actuation of the inhaler. Many adolescents and adults have been shown to use the devices incorrectly. The addition of an asthma spacer device (ASD) simplifies the use of a metered dose inhaler so that inhalation and actuation of the device do not need to occur simultaneously. National guidelines recommend the use of metered dosed inhalers with an asthma spacer device for home care. Traditionally, nebulizers have been used to deliver Albuterol in the emergency department. The benefit of utilizing an MDI with an ASD in the emergency department is that parents can be taught the correct uses of the devices and then be discharged with the devices that they used eliminating the need to fill prescriptions.

CLINICAL QUESTION: In children 12-60 months of age with a history of recurrent wheezing who present to the emergency department with wheezing is Albuterol delivered by a Metered Dose Inhaler with an Asthma Spacer Device equivalent to Albuterol delivered by a Nebulizer in generating clinical improvement as measured by the change in the pulmonary index score over 1 hour?

DESIGN/VALIDITY: This was a well-designed placebo controlled, double-blinded randomized equivalence trial that included 63 patients (MDI-ASD: 31, Nebulizer: 32) in the primary intention to treat analysis. Patients were randomized to one of 4 groups based on the device used (metered dose inhaler with an asthma spacer device or nebulizer) and the order in which the devices were used.

Each participant received 3 treatments and utilized both devices with each treatment. The nebulizer group received a standard Albuterol dose of 0.15 mg/kg while the MDI-ASD group received 1 puff for each 2 kilograms of body weight (0.05 mg/kg). The higher dose received in the nebulizer group could bias the study results in favor of the nebulizer group.

While there was no statistically significant difference in initial severity, 91% of patients in the MDI-ASD group were classified as moderate or severe and 78% of patients in the Nebulizer group were classified as moderate or severe. In addition, the median pulmonary index score at baseline was 2 points higher in the MDI-ASD group. The authors state that “unbalanced values in initial severity were taken into account in statistical analysis by considering only changes from baseline values.” This presumes that patients with a different illness severity respond similarly to treatment. Those with higher severity are more likely to demonstrate greater improvement. If this is true then the higher initial severity in the MDI-ASD group may bias the study results in favor of the MDI-ASD group.

All providers were trained in the study procedures. 44 (69%) of the patients were assessed by the principle investigator. Inter-rater reliability of the assessments was not assessed.

PRIMARY RESULTS: The 90% confidence interval for the median change in the Pulmonary Index Score from 0 minutes (pre-treatment) to 60 minutes (10 minutes after completion of the 3rd treatment) was -1 to +1 points. The authors defined equivalence as a 90% confidence interval within the range of -1.5 and +1.5 points. There was a statistically significant improvement in the median pulmonary index score for both groups over time. However, there was no difference in the median change in pulmonary index score from baseline for both treatment groups at 20 minutes (Difference: 0 points), 40 minutes (Difference: 0 points) and 60 minutes (Difference: 1 point MDI-ASD > Nebulizer).

6 patients required admission. 4 patients (2 in each treatment group) were admitted for treatment failure (defined as a post treatment pulmonary index score of > 6). The two other admissions were not related to study intervention. There was no statistically significant change in oxygen saturation though the mean oxygen saturation prior to treatment did not leave room for large improvements (MDI-ASD: 94.6%, Nebulizer: 95.9%). Parents reported the MDI-ASD as easier to use 94% of the time and better accepted by the child 62% of the time.

APPLICABILITY: It is likely that the study's results could be generalized to the emergency department setting for patient's meeting the study's inclusion and exclusion criteria. It is unclear if the French patient population differs from ours in ways that would affect the study outcomes. Is also unclear if the ease of use and acceptance evaluated by the parents would be similar in a population over 5 years of age. Patients from 1-2 years of age were included and bronchiolitis in this age group generally does not respond to bronchodilators potentially biasing the results in favor of equivalence. However, only patients with a prior history of wheezing were included.

The treatment regimen differed somewhat from ours. In is unclear why corticosteroids were not administered though it is unlikely that oral corticosteroids would influence the assessments within 60 minutes. Nebulizers were delivered with room air and not supplemental oxygen which is our practice.

AUTHOR'S CONCLUSION: "In 12 to 60 month-old children with recurrent wheezing, our data showed that efficacy of high-dose albuterol administered using the Asthma Spacer Device was equivalent to that of the nebulized albuterol. This main result confirms that Metered Dose Inhaler + Asthma Spacer Device "may be as effective as the nebulizer in delivering high doses of beta 2-agonists during severe exacerbations" as stated in the 1997 National Institutes of Health/World Health Organization guidelines. Given its tolerance, repeated 50 mcg/kg doses of albuterol administered through the Asthma Spacer Device should be considered for use in a hospital emergency department as first-line therapy."

POTENTIAL IMPACT: The use of a metered dose inhaler with an asthma spacer device was equivalent to the use of a nebulizer in producing clinical improvement over 1 hour with 3 consecutive treatments with Albuterol. Parents were more satisfied with use of the metered dose inhaler with an asthma spacer device. The benefit of utilizing an MDI with an ASD in the emergency department is that parents can be taught the correct uses of the devices and then be discharged with the devices that they used eliminating the need to fill prescriptions. The costs were not assessed.

APPENDIX: BASELINE CLINICAL ASTHMA SCORE

CLINICAL ASTHMA SCORE*			
SCORE	ACCESSORY MUSCLE SCORE	WHEEZE SCORE	DYSPNEA SCORE
0	No retractions	No wheezes and well	Absent dyspnea
1	Intercostal retraction	End expiratory wheezes	Normal activity & speech Minimal dyspnea
2	Intercostal and suprasternal retraction	Pan-expiratory ± inspiratory wheezes	Decreased activity, 5-8 word sentence, Moderate dyspnea
3	Nasal Flaring	Wheeze audible without stethoscope	Concentrates on breathing < 5 word sentence Severe dyspnea

*Shuh, J Pediatrics 1995, PubMed ID: 7699549

ASTHMA EXACERBATION: PREDNISONE VS DEXAMETHASONE

In children and adolescents ≤ 18 years of age presenting to the emergency department with an acute asthma exacerbation will a regimen of oral or intramuscular Dexamethasone when compared to a regimen of oral Prednisone or Prednisolone result in a reduction in unanticipated return visits to the emergency department (or clinic) or hospital admissions?

Rebecca Burton, M.D., Deborah Levine, M.D.
June 2014

Keeney GE, Gray MP, Morrison AK, Levas MN, Kessler EA, Hill GD, Gorelick MH, Jackson JL.

DEXAMETHASONE FOR ACUTE ASTHMA EXACERBATIONS IN CHILDREN: A META-ANALYSIS.

Pediatrics. 2014 Mar;133(3):493-9.
PubMed ID: 24515516

STUDY DEFINITIONS	
POPULATION	Inclusion: ≤ 18 years presenting to the ED or ambulatory care setting with acute asthma exacerbation. Exclusion: Patients who were hospitalized during the initial study encounter were not included in the analysis of return visits. Studies were excluded if they were not randomized clinical trials, or if they did not meet study quality criteria (Jadad score, Cochrane risk of bias tool, presence of industry sponsorship, whether intention to treat analysis was performed) as assessed by study authors. Setting: ED or ambulatory care setting, included studies published 1997-2008
INTERVENTION	Dexamethasone: Various dosing, routes and duration: 0.3 mg/kg IM x 1, 0.6 mg/kg IM x 1, 1.7 mg/kg IM x 1; 0.6 mg/kg PO x 1; or 0.6 mg/kg PO x 2 days
CONTROL	Prednisone/prednisolone PO: Various regimens, ranging from 1-2 mg/kg/day PO for 3-5 days
OUTCOME	Primary Outcome: Unanticipated return visits to the ED or clinic, or hospital admission Secondary Outcomes: Emesis in the ED or at home
DESIGN	Systematic review and Meta-analysis of randomized clinical trials

ARE THE RESULTS VALID?	
Did the review include explicitly and appropriate eligibility criteria?	Yes. The review included explicit and appropriate eligibility criteria, with well-defined inclusion and exclusion criteria as well as primary and secondary outcome measures. Study intervention was less well defined, with various regimens of dexamethasone and prednisone/prednisolone used (see above). During study selection, 667 potential studies were evaluated, with 661 excluded based on eligibility criteria, leaving 6 studies for analysis. It is likely that including only studies with identical intervention and control regimens was not feasible based on the small number of studies that met eligibility criteria for meta-analysis.
Was biased selection and reporting of studies unlikely?	Yes. Biased selection and reporting of studies is unlikely. The search for eligible studies was well-defined, reproducible, and not limited by language. The authors report examining reference lists from review articles and those included in the meta-analysis by hand in order to identify additional potential studies for inclusion. However, the authors do not mention any correspondence with experts in the field or members of the pharmaceutical industry. In addition, only one database, PubMed, was searched; it is possible that searching other databases, such EMBase and clinical trials registries may have produced additional potential studies for inclusion in the review. An assessment for publication bias was performed using statistical methods, including methods described by Peters, Egger, and also meta-influence plots.
Were the primary studies of high methodologic quality?	Yes. Study quality was assessed by two study authors independently using four criteria: 1. the Jadad score; 2. the Cochrane risk of bias tool; 3. presence of industry sponsorship; 4. and whether intention to treat analysis was performed. Both the Jadad score and the Cochrane risk of bias tool are validated instruments for assessment of study quality. Jadad scores ranged from 3-8 (modified Jadad score with criteria #3 and 4 above incorporated), with score <2.5 generally indicative of poor study quality (though interpretation of the modified score not as straightforward). Sensitivity analysis was not performed.
Were assessment of studies reproducible?	Interrater agreement for study quality between the two authors assessing study quality was good, with a Kappa of 0.90 (κ > 0.60 suggests good level of agreement beyond chance). Interrater agreement for assessment of study eligibility (i.e. meeting inclusion/exclusion criteria) was not reported.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

Yes. Heterogeneity was assessed both graphically (using Forest plots) and statistically.

Figure 2 is a Forest plot of the primary outcome (unanticipated return visit or hospital admission, reported as relative risk) results for the individual studies included in the meta-analysis, separated by time interval before assessment of primary outcome (5 days, 10-14 days, or 30 days). Point estimate of relative risk for most studies was around 1.0, supporting the null hypothesis of no statistically significant difference between prednisone/prednisolone and dexamethasone. In addition, there appears to be reasonable overlap of the confidence intervals in each of the groups. Confidence intervals for every study included relative risk of 1.0.

Figure 3 and 4 demonstrates Forest plots of the secondary outcomes of vomiting in the ED or vomiting at home. For all studies, point estimate of relative risk of emesis in the ED or at home is less than 1.0, suggesting decreased risk of vomiting in the dexamethasone group as compared to the prednisone/prednisolone group. There appears to be reasonable overlap of the confidence intervals in each of the groups for secondary outcomes as well.

To assess for heterogeneity statistically, study authors used the I^2 method. In general, $I^2 < 20\%$ suggests minimal variability, I^2 20%-50% suggests increased concern about variability, and $I^2 > 50\%$ suggest substantial heterogeneity between studies. For this meta-analysis, I^2 for the overall assessment of primary outcome was 0.0%, suggesting minimal/no heterogeneity. For other analyses in the meta-analysis (i.e. subgroup of studies reporting primary outcome at 5 days, analyses of emesis), I^2 ranged from 0.0% to 18.7%, suggesting minimal heterogeneity between studies for all outcomes assessed.

WHAT ARE THE OVERALL RESULTS OF THE REVIEW?

Primary Outcome: Unanticipated return visit to the ED or clinic, or hospital admission (“relapse”)
Relative Risk = Dexamethasone/(Prednisone or Prednisolone)

5 days
Relative Risk: 0.90, 95% CI (0.46, 1.78); I^2 0.0%

10-14 days
Relative Risk: 1.14, 95% CI (0.77, 1.67); I^2 0.0%

30 days
Relative Risk = 1.20, 95% CI (0.03, 56.9)
Only 1 study assessed the outcome at this time interval

Secondary Outcome: Vomiting
ED: Relative Risk = 0.29, 95% CI (0.12, 0.69); I^2 18.7%
Home: Relative Risk = 0.32, 95% CI (0.14, 0.74); I^2 4.2%

HOW PRECISE WERE THE RESULTS?

Confidence intervals for all relative risk assessments are presented above. All confidence intervals for primary outcome cross 1.0. in general, confidence intervals are moderately tight, suggesting good precision. The confidence interval for the primary outcome at 30 days (RR 1.20, 95% CI (0.03-56.93) is very wide (imprecise) as it is based upon the small sample size of a single study.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were all patient-important outcomes considered?	In general, most patient-important outcomes were considered. Additional outcomes that may have been helpful include 1. Patient compliance with treatment regimen at home, particularly because Dexamethasone may improve compliance with dexamethasone (shorter course, more palatable, less vomiting) and it longer half-life supports fewer doses. 2. Patient and/or parent satisfaction
Are any postulated subgroup effects credible?	No subgroup effects were postulated.
What is the overall quality of the evidence?	The overall quality of the evidence is moderate. The study is limited by several factors, including different regimens of dexamethasone (i.e. IM versus PO, different doses), and to a lesser extent prednisone/prednisolone; different time points for reporting of outcomes; and paucity of studies, making subgroup analyses unfeasible.
Are the benefits worth the costs and potential risks?	Potential benefits of dexamethasone as compared to prednisone/prednisolone include improved palatability, decreased vomiting, a postulated improvement in patient compliance and parent/patient satisfaction, and decreased healthcare costs. Long term effects of administration of a one or two doses of dexamethasone for acute asthma exacerbation have not been well studied though unlikely

CLINICAL BOTTOM LINE

BACKGROUND: Acute asthma exacerbations are common in the pediatric population, accounting for an estimated 2% of all ambulatory care and emergency department visits by patients ≤18 years of age. Bronchodilators (such as Albuterol) and corticosteroids have become the mainstays of therapy for acute asthma exacerbations. Two treatment options for outpatient corticosteroid administration that are currently available for children presenting with mild to moderate asthma exacerbation include oral Prednisone/Prednisolone and intramuscular or oral Dexamethasone. Though Prednisone/Prednisolone has long been considered the gold standard, Dexamethasone has been proposed to be an equivalent therapy. Postulated benefits of dexamethasone include improved palatability resulting in less vomiting, shorter duration of treatment and improved compliance.

CLINICAL QUESTION: In children and adolescents ≤ 18 years of age presenting to the emergency department with an acute asthma exacerbation will a regimen of oral or intramuscular Dexamethasone when compared to a regimen of oral Prednisone or Prednisolone result in a reduction in unanticipated return visits to the emergency department (or clinic) or hospital admissions?

DESIGN/VALIDITY: This study is a meta-analysis of 6 randomized clinical trials assessing use of Prednisone/Prednisolone as compared to Dexamethasone for treatment of acute asthma exacerbation in children ≤ 18 years presenting to either the emergency department or ambulatory care setting. 1,129 patients were included in the primary analysis. The analysis determined relative risk (Dexamethasone/ Prednisone) for the primary outcome of “relapse,” defined as unanticipated return visit to the ED or clinic, or hospital admission and the secondary outcome of vomiting in the ED or at home.

This study was well designed without major methodologic flaws or validity concerns. Study inclusion and exclusion criteria were well defined and appropriate, selection bias seems unlikely, study quality of included studies appears to be high, and assessment of study quality by individual authors was highly reproducible. One significant limitation is the variety of regimens (dose, route and duration) used in each study. 3 studies used intramuscular Dexamethasone and the other 3 studies oral Dexamethasone, as Compared to PO Prednisone/Prednisolone. Dosing also varied among studies for both interventions.

PRIMARY RESULTS: This study demonstrated no statistically significant difference between the Dexamethasone group and the Prednisone/Prednisolone group for the primary outcome of relapse (unanticipated return visit to the ED or clinic, or hospital admission). This result, reported as relative risk (Dexamethasone/Prednisolone), was observed at all time points used for assessing outcome: At 5 days, relative risk = 0.90, 95% CI (0.46, 1.78); at 10-14 days: relative risk = 1.14, 95% CI (0.77, 1.67) and at 30 days (based on a single study): relative risk = 1.20, 95% CI (0.03, 56.93). For the secondary outcomes of vomiting in the ED and at home, the meta-analysis demonstrated decreased risk of vomiting in both settings for the Dexamethasone group as compared to the Prednisone/Prednisolone group: In the ED: relative risk = 0.29, 95% CI (0.12, 0.69) and at home: relative risk = 0.32, 95% CI (0.14, 0.74).

APPLICABILITY: This study is largely generalizable to the population of pediatric patients with asthma who are managed in the emergency department. Additional outcomes that might prove insightful include: patient compliance with treatment regimen at home and patient and/or parent satisfaction.

AUTHOR'S CONCLUSION: "Based on our findings, emergency physicians should consider single or 2-dose dexamethasone regimens over 5-day prednisone/prednisolone regimens for the treatment of acute asthma exacerbation."

POTENTIAL IMPACT: This meta-analysis suggests that Dexamethasone (intramuscularly or oral) may be an equivalent treatment option to oral Prednisone/Prednisolone for treatment of acute asthma exacerbation in children ≤ 18 years of age who present to the emergency department. It also suggests that oral or intramuscular Dexamethasone results in less vomiting in the ED and at home as compared to oral Prednisone/Prednisolone.

The analysis was limited to some extent by a paucity of studies (n=6), various regimens of both Dexamethasone and Prednisone/Prednisolone, and different time points for assessment of outcomes. Several questions remain unanswered

1. Whether results would translate to non-ED settings
2. Whether intramuscular and oral dexamethasone are equally effective;
3. What the optimal dose of dexamethasone is (range 0.3 mg/kg to 1.7 mg/kg used in studies)
4. Whether a single oral dexamethasone dose for 1 day is equivalent to 2 days
5. Whether there are differences in efficacy/palatability with different formulations of oral prednisone/ prednisolone
6. Whether there are any differences in patient/parent satisfaction between the two regimens

Further studies should attempt to address these questions. PEM physicians can consider prescribing a single or 2-dose Dexamethasone regimen rather than a 5-day course of Prednisone/Prednisolone regimen for treatment of acute asthma exacerbation. If a second dose of the Dexamethasone could be provided upon discharge this would eliminate non-compliance because of prescriptions that are not filled.

ASTHMA EXACERBATION: SINGLE DOSE DEXAMETHASONE

In pediatric patients who present to the ED with an acute asthma exacerbation, is a single dose of oral Dexamethasone non-inferior to oral Prednisolone for 3 days as measured by the Pediatric Respiratory Assessment Measure (PRAM) at day 4 after the initial visit?

Katrina Knapp D.O., Laura Papadimitropoulos M.D.
June 2016

Cronin JJ, McCoy S, Kennedy U, An Fhailí SN, Wakai A, Hayden J, Crispino G, Barrett MJ, Walsh S, O'Sullivan R.

A RANDOMIZED TRIAL OF SINGLE-DOSE ORAL DEXAMETHASONE VERSUS MULTIDOSE PREDNISOLONE FOR ACUTE EXACERBATIONS OF ASTHMA IN CHILDREN WHO ATTEND THE EMERGENCY DEPARTMENT.

Ann Emerg Med. 2016 May;67(5):593-601
PubMed ID: 26460983

STUDY DEFINITIONS	
POPULATION	Inclusion: Children 2-16 years old with history of asthma (defined as 1 previous episode of beta 2 agonist responsive wheeze or previous diagnosis of asthma made by clinical or specialist) presenting to the ED with an acute asthma exacerbation. Asthma exacerbation defined as; any or all of the following clinical features; dyspnea, wheeze, acute cough, increased work of breathing, increased requirement for beta-2 agonist from baseline use, or SaO2 < 95%. Exclusion: Children with critical or life-threatening asthma exacerbation (defined as having any 1 of the following; confusion or drowsiness, maximal accessory muscle use or recession, poor respiratory effort, exhaustion, silent chest, cyanosis, SaO2 less than 90% on RA, marked tachycardia, PTX, unable to verbalize normally), active varicella or herpes simplex infection, concurrent infection with RSV, temp > 39.5 C, use of oral or intravenous corticosteroids in the previous 4 weeks, concurrent stridor, galactose intolerance, Lapp-lactase deficiency, history of TB exposure, or significant comorbid disease Setting: Single Children's hospital (Ireland), 7/11 to 6/12
INTERVENTION	Dexamethasone: Single oral dose of 0.3 mg/kg (maximum dose 12 mg)
CONTROL	Prednisolone: 1 mg/kg per day (maximum dose 40 mg) once daily for 3-days (Both Medications were provided to the patient to take home)
OUTCOME	Primary Outcome: Mean PRAM score at day 4 (See Appendix). 5 components with a maximum total score of 12); suprasternal retractions (0-2), scalene muscle contraction (0-2), air entry (0-3), wheezing (0-3), and SaO2 (0-2)) Secondary Outcomes: Change in PRAM score from ED discharge to follow-up PRAM score at ED discharge Hospital admission from ED on day 1 ED length of stay Unscheduled visits to health care provider for asthma or respiratory symptoms within 14 days of enrollment Readmission to the hospital within 14 days after enrollment Administration of further corticosteroids within 14 days after enrollment.
DESIGN	Interventional: Randomized clinical trial (non-inferiority hypothesis)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Randomized was in permuted blocks of 12 subjects.
Was randomization concealed?	Likely Yes. The randomization process was designed by the study statistician and kept in a locked storage cupboard in the hospital pharmacy department. The recruiting clinician took the next available numbered envelope from the pre-randomized pack of study envelope. It does not appear that there was an opportunity to bias the randomization and allocation process to the study groups though this was not explicitly stated.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. (Table 2). Baseline demographic characteristics, except for sex distribution, were similar between the 2 groups. (There more male patients in the Prednisone group than the Dexamethasone group; 61.8% vs 74.6%). No significant difference in PRAM score at initial ED clinical assessment or symptom durations.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	This was an open label study. Investigators, participants and parents were aware of which medication they received. Patients and families were instructed to not reveal the medication received to the clinician measuring the PRAM score on day 4 so that the primary outcome was assessed in a blinded manner.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDY'S CONCLUSION?	
Was follow-up complete?	Yes. There was a low loss to follow-up rate. 120/123 (97.5%) of the Dexamethasone group and 115/122 (94.2%) of the Prednisone group were followed up at Day 4.
Were patients analyzed in the groups to which they were randomized?	Yes. An intention to treat analysis was performed. There was no per protocol analysis. A per protocol analysis would include only those patients who received the study medication. A total of 14 patients vomited their Prednisone (7 on day 1, 7 on day 2, and 6 on day 3). A per protocol analysis would have excluded those patients who vomited. If the patient vomited the medication in the ED within 30 minutes of administration a second dose was given. If the patient vomited again within 30 minutes of administration, no further dose was administered if the vomiting occurred at home.
Was the trial stopped early?	No. The trial was not stopped early.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Primary Outcome: Mean PRAM score on Day 4
Dexamethasone: 0.91 (SD 1.16), n = 120
Prednisolone: 0.91 (SD 1.52), n = 115
Mean Difference (DEX - PRED) = -0.005, 95% CI (-0.35, 0.34)

Subgroup Analysis: (Table 3):
Dexamethasone was non-inferior to Prednisolone when subgroups based on age, gender, re-enrollment and severity of asthma exacerbation were analyzed.

Secondary Outcomes: (Table 4)
Further systemic steroids administered: DEX > PRED
Hospital Admission from ED on Day 1: No difference
Length of admission, mean SD, days: No difference
Return visit to PCP within 14 days: No difference
Hospital admission post d/c within 14 days: No difference
Number of days of restricted activity: No difference
Number of subjects who missed school: No difference
Number of parental workdays: No difference

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Mean difference (DEX - PRED) = -0.005 (95% CI -0.35, 0.34)
The authors considered Dexamethasone to be non-inferior to Prednisolone if the mean PRAM score at day 4 for the Dexamethasone group was not more than 1 point higher than for the Prednisolone group. Since the lower limit of the confidence interval is not below -1 a single dose of oral Dexamethasone is non-inferior to a 3-day course of oral Prednisolone as measured by the mean PRAM score on day by the authors criteria.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	The patients baseline PRAM score average between groups was about 4.5 (mild/moderated exacerbation), which is similar to our asthmatic population in the ED.
Were all clinically important outcomes considered?	All clinically important outcomes were considered. A per protocol analysis excluding those who vomited the medication would have been helpful. In addition, a subgroup analysis excluding patients who were hospitalized, would have made the results specific to those discharged from the ED.
Are the likely treatment benefits worth the potential harm and costs?	A single oral dose of Dexamethasone is inexpensive and would ensure compliance but not requiring parents to fill a prescription and administer the medication at home. In addition, oral Prednisolone has a bitter taste and children are more likely to vomit it. In this study, 14 (12%) patients in the Prednisolone group vomited at least once while 0 patients in the Dexamethasone group vomited. NNT (1/0.12 = 8.3%). For every 8.3 patients treated with Prednisolone 1 additional patient will vomit compared to Dexamethasone

CLINICAL BOTTOM LINE

BACKGROUND: Corticosteroids have been shown to reduce asthma relapses, hospital admissions, and the amount of beta agonist bronchodilators that are required. The most common oral steroid medication given for children with an acute asthma exacerbation is Prednisone/Prednisolone. Unfortunately, Prednisolone is frequently vomited and compliance with discharge medications is often less than optimal. In addition, a 3-5 day course is typically prescribed. Dexamethasone has the potential benefits of a longer half-life and better tolerance. A 3-day course of oral Prednisolone is recommended by the British asthma management guidelines

CLINICAL QUESTIONS: In pediatric patients who present to the ED with an acute asthma exacerbation is a single dose of oral Dexamethasone (0.3 mg/kg, max 12 mg) non-inferior to oral Prednisolone (1mg/kg, max 40 mg) for 3 days as measured by the Pediatric Respiratory Assessment Measure (PRAM) at day 4 after the initial visit?

DESIGN/VALIDITY: This was a prospective, open-labeled, randomized, controlled study which included 245 patients in the primary intention to treat analysis. It was well designed but did have some minor risks of bias concerns. Since the study was open the participants and the initial treating physician were aware which treatment the patients were receiving. However, the assessment of the primary outcome on day 4 was blinded to the treatment received. The study also utilized a Dexamethasone dose which is approximately half of what we administer.

PRIMARY RESULTS: The mean PRAM score at day 4 for Dexamethasone group was 0.91 (SD1.16) and for the Prednisolone group was 0.91 (SD 1.52). In an intention to treat analysis, the mean difference (Dexamethasone - Prednisolone) was -0.005 (95% CI -0.35, 0.34). Since the lower limit of the confidence interval is not below -1, a single dose of oral Dexamethasone is non-inferior to a 3-day course of oral Prednisolone by the authors criteria. It would have been helpful to have a per protocol analysis to determine the effect of vomiting Prednisolone on the primary outcome. There were 14 patients (12%) total vomited at least one dose in the Prednisolone group while there were no patients who vomited in the Dexamethasone group. If they had vomited a dose in the ED within 30 minutes of receiving it, they were given a second dose but the number of patient who required an additional attempt and whether they tolerated the 2nd dose was not reported. Ultimately it is difficult to determine how many patients actually received all 3 doses in the Prednisolone group. It is unclear why the study included admitted patients in the primary analysis. There were 18 (15%) admitted patients in the Dexamethasone group and 16 (14%) were admitted in the Prednisolone group. It would have been helpful to have a subgroup analysis excluding those patients who were admitted.

APPLICABILITY: It is difficult to apply the study's results to the patients that we treat in the emergency department. The patients in this study had extremely high compliance with follow up and were given the medication to take home rather than provided with a prescription. In our patient population, we have a poor compliance rate with follow up and approximately 40% of patients will fill their prescriptions. In addition, we use a higher dose (0.6 mg/kg vs 0.3 mg/kg) of Dexamethasone. Some physicians give one dose of Dexamethasone while others provide a prescription for a second dose on day 2. This is equivalent to a 5-day course of Prednisone. In addition, we dose Prednisolone at 1-2 mg/kg/day for 5 days rather the 1 mg/kg/day for 3 days.

AUTHOR'S CONCLUSION: "In conclusion, this randomized controlled trial of steroids in children with acute asthma who attended the ED found no significant difference between a single dose of oral dexamethasone (0.3 mg/kg) and a 3-day course of oral prednisolone (1 mg/kg per day). However, more patients in the DEX group were treated with further steroids during the study. According to our findings, it may be possible to safely use a single dose of oral dexamethasone to simplify the ED treatment of children with acute asthma exacerbation."

POTENTIAL IMPACT: It is hard to generalize the results of this study to our practice based on the difference in dosing and duration of therapy. It is unclear if a single dose of Dexamethasone would be non-inferior to Prednisolone given for 5 days and unclear if a second dose of Dexamethasone on day 2 would be warranted. Dexamethasone is better tolerated and a single dose of Dexamethasone in the ED would ensure compliance.

APPENDIX: PRAM SCORE

PEDIATRIC RESPIRATORY ASSESSMENT MEASURE (PRAM) SCORE				
	0	1	2	3
Suprasternal muscle contraction	Absent		Present	
Scalene muscle contraction	Absent		Present	
Air entry*	Normal	Decreased at bases	Widespread decreased	Absent, Minimal
Wheezing*	Absent	Expiratory only	Inspiratory and Expiratory	Audible without stethoscope OR Silent chest with minimal air entry
SaO2 (%)	≥ 95	92-94	< 92	
*In case of asymmetry, the worst lung is rated. Mild exacerbation = 1-3, Moderate = 4-7, Severe = 8-12				

Ducharme FM, Chalut D, Plotnick L, et al.
The Pediatric Respiratory Assessment Measure: A Valid Clinical Score for Assessing Acute Asthma Severity from Toddlers to Teenagers.
J Pediatr. 2008;152: 476-480; 80.e1. PubMed ID: 18346499

ASTHMA EXACERBATION: TERBUTALINE

In children age 2-17 years, with a moderate to severe asthma exacerbation who are receiving continuous Albuterol, Ipatropium and Corticosteroids does the addition of intravenous Terbutaline when compared to Placebo (normal saline) improve exacerbation severity (CASS score over 24 hours?

Katherine Fullerton, M.D., Adriana Manikian, M.D.

August 2007

Bogie AL, Towne D, Luckett PM, Abramo TJ, Wiebe RA.

Comparison of Intravenous Terbutaline Versus Normal Saline in Pediatric Patients on Continuous High-Dose Nebulized Albuterol for Status Asthmaticus.

Pediatr Emerg Care. 2007 Jun;23(6):355-61.
PubMed ID: 17572517

STUDY DEFINITIONS	
POPULATION	Inclusion: 2-17 years, moderate-severe asthma exacerbation, failed to improve after ≥ 3 consecutive nebulized Albuterol (5 mg)/Ipratropium bromide (500 mcg), placed on continuous high-dose nebulized Albuterol, require intravenous beta-agonist therapy by ED attending, admit to PICU Exclusion: 1. Terbutaline allergy 2. History cardiac dysrhythmia 3. Intubated prior to nebulized Albuterol x 3 4. Pregnant 5. Previously enrolled 6. Transfer out due to lack of PICU bed 7. Fixed obstructive cardiopulmonary lesions. Setting: Single Children's Hospital ED, 5/2000-3/2001
INTERVENTION	Terbutaline: Loading dose of 10 mcg/kg/minute over 10-20 minutes, followed by a continuous infusion of 1 mcg/kg/minute.
CONTROL	Placebo: Normal saline, equivalent volume
CO-INTERVENTIONS	1. At attending physician discretion, the study drug (terbutaline or placebo) increased to 2 mcg/kg/min. Further deterioration of resulted in an increase in the study drug to 4 mcg/kg/minute 2. Aminophylline: Indicated if study drug was increased to 4 mcg/kg/minute. (Dose of aminophylline at pediatric intensivist discretion) 3. Weaned from the study medication at discretion of the attending physician. 4. Methylprednisolone: 2 mg/kg loading dose then 1 mg/kg every 6 hours. 5. Continuous high-dose nebulized Albuterol: 10 mg/hour (< 20 kg), 15 mg/hour (20-40 kg), 20 mg/hour (> 40 kg) 6. Ipratropium bromide nebulization Q6H: 250 mcg (≤ 10 kg), 500 mcg (> 11kg) 7. Normal saline bolus 20 ml/kg then maintenance intravenous fluids
OUTCOME	Primary Outcome: Clinical asthma severity score (CASS) score over 24 hours (See Appendix) Secondary Outcomes: 1. Hours on continuous nebulized Albuterol 2. Length of PICU stay 3. Need for Aminophylline 4. Intubation 5. Adverse events: Dysrhythmias, troponin elevation, EKG ST changes
DESIGN	Interventional: Randomized clinical trial.

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Randomization was done on a per-patient basis by the study pharmacist using a table of random numbers. Of the 49 patients enrolled, 46 were included in the analysis, 25 were randomized to the treatment group and 21 to the placebo group.
Was randomization concealed?	Yes. The pharmacy dispensed a vial of loading dose and continuous infusion of either Terbutaline or Placebo (normal saline). The study drug (Terbutaline) and Placebo (normal saline) were similar in consistency, smell and color. It does not appear that there was an opportunity to bias the allocation process.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Patients were similar in respect to age, ethnicity and initial CASS score. However, historical severity of asthma was higher in the Terbutaline group. Terbutaline group: 32% mild, 60% moderate, 8% severe. Placebo group: 62% mild, 29% moderate, 10% severe. If patients with more severe illness were less likely to responds then this could potentially bias the study results against Terbutaline.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Only the study pharmacist was aware of group allocation. However, since Terbutaline is sympathomimetic it is possible that patients in the treatment group were more tachycardic and therefore the potential awareness of group allocation by clinicians existed. Unblinding was of the study drug occurred at 24 hours or sooner if the patient experienced a life-threatening complication.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Patients were either in the ED or in the PICU during the study period. 10% (5/49) did not complete the study. 1 patient in the Terbutaline group was removed due to a dysrhythmia.
Were patients analyzed in the groups to which they were randomized?	Yes. The patients who completed the study were analyzed in the groups they were randomized to. 2 of the 5 patients who did not complete the study were not included and limited data from the other 3 were used in the analysis.
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 49, 45 included in the primary analysis

Primary Outcome: Mean improvement in CASS score over 24 hours (Figure 1)
Terbutaline group: 6.5 points (baseline 11.4)
Placebo group: 4.8 points (baseline 10.8)
Mean difference: 1.7 points, p = 0.073, Confidence interval not provided

Secondary Outcomes:

Mean Duration on Continuous Nebulized Albuterol
Terbutaline group: 38.2 hours, SD 21.2 hours
Placebo group: 51.9 hours, SD 49.1 hours
Mean difference: 13.7 hours (p = 0.25), Confidence interval not provided

PICU Length of Stay
Terbutaline group: 43.9 hours, SD 43.9 hours
Placebo group: 56.9 hours, SD 55.9 hours
Mean difference: 16 hours (p = 0.34), Confidence interval not provided

ADVERSE EVENTS

	TERBUTALINE	PLACEBO
Aminophylline use	9	5
↑ Troponin 12 or 24 hours*	6	0
Significant arrhythmia	1	0
ST-Segment changes	2	0
Hypotension	8	9

*Baseline Troponin levels were elevated in the Terbutaline group (2.0 vs 1.3)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

There was not a statistically significant difference in the mean CASS score (1.7 points) over 24 hours (p = 0.073). However, the authors considered a 1 point difference in CASS score to be clinically significant in their sample size determination.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. We see patients frequently in this age group with moderate to severe asthma exacerbations. However, Magnesium sulfate is also used in the majority of our patients.
Were all patient important outcomes considered?	Yes. However, objective measures such as improvement in peak expiratory flow rate may have been useful. In addition, inter-rater reliability of the CASS score was not presented.
Are the likely treatment benefits worth the potential harm and costs?	No. The addition of a continuous infusion of intravenous Terbutaline to a regimen of continuous Albuterol, Ipatropium bromide and intravenous steroids does not add a statistically significant benefit to patients for clinical improvement (modified CASS), length of PICU stay, or length of time on continuous albuterol. In addition, in this small sample, several patients treated with Terbutaline had evidence of cardio-toxicity as demonstrated by ST elevations, a dysrhythmia, and troponin elevations.

CLINICAL BOTTOM LINE

BACKGROUND: The efficacy of intermittent or continuous inhaled beta agonists and oral or intravenous corticosteroids has been well established in the treatment of status asthmaticus. A variety of agents, such as Magnesium, Ketamine and intravenous beta agonists have been suggested as useful adjuncts in the pediatric patients unresponsive to this standard therapy. Terbutaline is a beta-adrenergic agonist with selectivity for the beta 2 receptors, resulting in bronchial smooth muscle relaxation and inhibition of mast cell inflammatory mediator release. It has been used to treat asthma subcutaneously, via nebulization and as a continuous infusion.

CLINICAL QUESTION: In children age 2-17 years, with a moderate to severe asthma exacerbation who are receiving continuous Albuterol, Ipatropium and Corticosteroids does the addition of intravenous Terbutaline when compared to Placebo (normal saline) improve the CASS score (measure of asthma exacerbation severity) over 24 hours?

DESIGN/VALIDITY: This was a well-designed randomized clinical trial of intravenous Terbutaline for moderate to severe pediatric asthma exacerbation that enrolled 49 patients, 45 of which were included in the primary analysis. The primary validity concern is the study's small sample size. In addition, objective measures such as improvement in peak expiratory flow rate may have been useful though they may have been difficult to obtain from the sickest asthmatics.

PRIMARY RESULTS: For the primary outcome of the mean improvement in CASS score (see Appendix) over 24 hours, the Terbutaline group had a mean decrease in 6.5 points (baseline 11.36) and the placebo group had a mean decrease of 4.8 points (Mean difference: 1.7 points). There was not a statistically significant difference in the mean CASS score (1.7 points) over 24 hours ($p = 0.073$). However, the authors considered a 1 point difference in CASS score to be clinically significant in their sample size determination.

There was no statistically significant difference between the Terbutaline and Placebo groups for the secondary outcome measures of: duration of therapy with continuous albuterol, use of Aminophylline or PICU length of stay.

6 patients in the Terbutaline group and 0 patients in the Placebo group had elevated Troponin levels at 12 or 24 hours. However, baseline Troponin levels were elevated above normal in the Terbutaline group (Terbutaline 2.0, Placebo1.3). One patient in the Terbutaline group had a significant arrhythmia (frequent supraventricular beats and atrial bigeminy) which ceased after discontinuation of Terbutaline.

APPLICABILITY: The study results are likely generalizable to patients meeting the study's inclusion and inclusion criteria. However, no patients received Magnesium sulfate which is commonly used in asthma patient's refractory to nebulized beta agonist and corticosteroids. In addition, inter-rater reliability of the CASS score was not assessed.

AUTHOR'S CONCLUSION: "In conclusion, no statistically significant differences between outcome measures were identified when comparing the use of intravenous terbutaline versus normal saline in pediatric patients on high-dose continuous b-agonist therapy. However, a trend toward more rapid improvement was noted in those patients receiving intravenous terbutaline.

The authors would recommend further study using either continuous or bolus therapy with intravenous terbutaline for acute severe asthma in pediatric patients already on continuous high-dose nebulized b-agonist therapy to deter- mine safety and efficacy."

POTENTIAL IMPACT: In this randomized, placebo controlled trial, the addition of intravenous Terbutaline to continuous Albuterol, Ipatropium and corticosteroids, in pediatric patients with a moderate to severe asthma exacerbation, did not demonstrate a statistically significant benefit over 24 hours as demonstrated by the CASS score. In addition, there was no difference in the study's secondary outcome measures. Given the lack of benefit and the potential for significant cardiotoxicity, this study does not support the routine use of intravenous terbutaline in this population. These conclusions should take into account the study's small sample size.

APPENDIX: CASS SCORE

CLINICAL ASTHMA SEVERITY SCORE (CASS)					
SCORE	Respiratory Rate	Room air Saturation*	Auscultation	Retractions	Dyspnea**
0	< 30	97-100%	None	None	None
1	30-45	94-96%	End Expiration	+/-	Full sentences
2	46-60	91-93%	All Expiration	++	Partial Sentences
3	> 60	< 91%	I and E without stethescope	+++	Single words/grunts
*Off oxygen for 5 minutes or until saturation < 91% **Nurse's or parent's subjective assessment					

BRONCHIOLITIS:
APNEA RISK FACTORS

In Infants < 6 months of age who are admitted with bronchiolitis can clinical and demographic features predict the risk of in-hospital apnea?

Marc Auerbach M.D., Michael Tunik M.D.
December 2006

Willwerth BM, Harper MB, Greenes DS.

IDENTIFYING HOSPITALIZED INFANTS WHO HAVE BRONCHIOLITIS AND ARE AT HIGH RISK FOR APNEA

Ann Emerg Med. 2006 Oct;48(4):441-7.
PubMed ID: 16997681

STUDY DEFINITIONS	
POPULATION	Inclusion: < 6 months of age, admitted to the hospital. Bronchiolitis defined as wheezing, crackles, or respiratory distress (manifested as retractions or respiratory rate > 60 breaths per minute) Exclusion: Infiltrate on chest XRAY, Identifiable anatomic, metabolic, or infectious cause of the respiratory findings. Admitted in the prior month for bronchiolitis Setting: Single Pediatric hospital ED, 11/1995-6/2000,
PROGNOSTIC FACTORS	History and physical examination in the ED, results of radiologic and viral testing, and the hospital course. Risk criteria for apnea: High = ≥ 1 criteria. Low risk = 0 criteria 1. Age less than 1 month in full-term infants 2. Postconceptional age less than 48 weeks in preterm infants 3. Parent or clinician witnessed apnea with this illness before hospital admission In-hospital Apnea: Physician documented respiratory pauses while an inpatient Patients undergoing tracheal intubation in the ED because of recurrent episodes of apnea were also considered as in-hospital apnea.
CONTROL	Patients admitted with bronchiolitis without apnea
OUTCOME	Association of potential predictors with in-hospital apnea Test characteristics of predefined apnea risk criteria
DESIGN	Observational: Retrospective cohort study

HOW SERIOUS WAS THE RISK OF BIAS?	
Was the sample of patients in a study representative?	Unclear. We can't tell if these patients are at similar points in their disease process. They presented to the ED with clinical bronchiolitis and then were all admitted. There was no documentation of days of illness, severity of disease, or admission criteria.
Were the patients classified into prognostically similar groups?	Unclear. Moderately homogenous with respect to prognosis. Inclusion based on age, admission, ICD-9 coding, and then by meeting the pre-defined diagnostic criteria for bronchiolitis upon ED chart review. These patients would be better defined if we had specific criteria for admission. Since the duration of illness could be associated with the outcome. There was no adjustment for prognostic factors.
Was follow-up sufficiently complete?	No. Patients were only followed to hospital discharge. No attempt was made to follow patients after discharge. The authors did not discuss the hospitals criteria for discharge, duration of hospitalization, or course in the hospital.
Were study outcome criteria objective and unbiased?	Yes. The investigators provided a clear and sensible definition of apnea before the study started. Data was retrospectively abstracted on a standardized form from the patient chart by a single un-blinded author who was aware of the research hypothesis. Apnea was loosely defined because "There was a lack of exact documentation related to cessation of breathing, hypoxia, cyanosis or bradycardia." It is not clear how the reviewers would have been blind to predictor variable data when screening inpatient data for apnea. A random sample of 6% of patients were re-reviewed by another physician who was unaware of the study hypothesis. All patients who had apnea were reviewed and twice as many patients without apnea were reviewed. The Kappa statistics for met studies inclusion criteria 0.91 and for apnea 0.96 indicates a high level of inter-rater reliability.

WHAT ARE THE RESULTS?

HOW LIKELY ARE THE OUTCOMES OVER TIME?

The risk of apnea in this group of hospitalized infants with bronchiolitis
19/691 = 2.7%, 95% CI (1.7, 4.3%)

Individual Predictors (Table 2)
Younger infants with a lower mean post-conceptional age or lower median gestational age were at increased risk of apnea
Preterm: Odds Ratio 12.3 (4.0,37.6)
Parent witnessed apnea: Odds Ratio 20.5 (7.5, 55.9)
Clinician witnessed apnea: Odds Ratio 460 (88, 2,423)

Prediction Rule (Table 4)
High risk criteria (38% of patients)
1. Full term and < 4 weeks: 18%
2. Preterm and < 48 weeks: 18%
3. Witnessed apnea by parent: 4.5%, clinician: 1.9%

Sensitivity	100% (82, 100%)
Specificity	64% (60, 67%)
Predictive Value Positive Rule	7% (4, 11%)
Predictive Value Negative Rule	100% (99, 100%)

HOW PRECISE ARE THE ESTIMATES OF LIKELIHOOD?

The confidence intervals for the individual predictors and the rule performance are listed above. The low rate of apnea results in very wide confidence intervals for sensitivity.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients and their management similar to those in my practice?	Unclear. We do not have a standard demographic “Table 1”. We know that it is tertiary care university hospital ED so likely somewhat similar to Bellevue.
Was the follow-up sufficiently long?	Unclear. We do not know if any discharged patients had apnea.
Can I use the results in the management of patients in my practice?	Yes. You could discuss this data with family. It is important to say that it needs to be repeated and may not be valid. Could use as a reason for or against and admission with a family that either wants to stay or go.

CLINICAL BOTTOM LINE

BACKGROUND: Traditionally, respiratory distress, oxygen requirement and dehydration are the primary criteria used to determine the need for admission in the infant with bronchiolitis. In addition, the ED physician must consider the risk of subsequent apnea in this age group. While the literature has clearly documented the risk of apnea in this age group, specific predictors of apnea have not been clearly identified. The authors of this study attempt to identify clinical and demographic predictors of apnea to aid in the clinical decision-making process. Specifically, they a priori defined 3 high risk factors for risk of subsequent apnea: Full term and < 4 weeks, Preterm and < 48 weeks and witnessed apnea (by the caregiver or the clinician).

CLINICAL QUESTION: In Infants < 6 months old who are admitted with bronchiolitis can clinical and demographic features predict the risk of in-hospital apnea?

DESIGN/VALIDITY: This was a retrospective cohort study of an existing database that included 691 patients in the primary analysis. 19 (2.7%) had in-hospital apnea, The primary validity concerns in this study is the retrospective nature of the data collection and the lack of predefined admission criteria. Since these patients were all admitted it is difficult to apply the predictors to a group of patients who do not fulfill criteria for admission. In addition, it would have been helpful to look at traditional admission criteria (respiratory distress, oxygen requirement, dehydration) and significant underlying illness (respiratory, cardiac) as additional predictors.

PRIMARY RESULTS: The use of this rule would have identified all infants with subsequent apnea. The authors decision rule had a sensitivity of 100%, 95%CI (82, 100%) and a predictive value of a negative rule of 100%, 95% CI (99,100%). This is a first step in identifying risk factors for apnea in the infant with bronchiolitis. 9 of the 19 patients with in-hospital apnea had a parent or clinician witnessed apnea prior to admission. It is very unlikely that these patients would ever be discharged but the witnessed apnea would likely prompt admission to a monitored setting. Only 2 of the remaining 10 who had in-patient apnea were full term. The specificity of the rule was only 64%. The application of the rule to infants who do not otherwise meet admission criteria could potential increase the admission rate.

APPLICABILITY: This was a decision rule that was neither derived statistically or validated. It should not be used clinically at this time. Without a clear definition of why these infants were admitted it is difficult to determine who to apply the rule to.

AUTHOR'S CONCLUSION: "In summary, we have found apnea to have a rate of 2.7% among young hospitalized infants with bronchiolitis. We have used a retrospective data set to validate a set of risk criteria, developed a priori, that successfully identifies infants with bronchiolitis who are at risk to develop subsequent apnea. If an infant with bronchiolitis is full term and older than 1 month or preterm and greater than 48 weeks post-conception and has had no previous apnea with this illness, the risk of subsequent apnea is low."

POTENTIAL IMPACT: Further prospective study is needed to derive and validate a clinical prediction rule that could be confidently utilized by clinicians to aid in the decision to admit an infant with bronchiolitis due to the risk of subsequent apnea.

BRONCHIOLITIS:
DECOMPENSATION RISK FACTORS

In otherwise healthy infants and toddlers less than 24 months of age admitted to the general inpatient unit with a diagnosis of bronchiolitis, are there demographic and clinical factors identifiable in the emergency department associated with decompensation requiring ventilatory support?

Shweta Iyer, M.D., Rebecca Burton, M.D
February 2018

Dadlez NM, Esteban-Cruciani N, Khan A, Douglas LC, Shi Y, Southern WN.

RISK FACTORS FOR RESPIRATORY DECOMPENSATION AMONG HEALTHY INFANTS WITH BRONCHIOLITIS.

Hosp Pediatr. 2017 Sep;7(9):530-535.

PubMed ID: 28830913

STUDY DEFINITIONS	
POPULATION	Inclusion: < 24 months, primary/secondary diagnosis of bronchiolitis, admit to the general pediatric inpatient unit through the ED Exclusion: Ventilatory support required in the ED Not evaluated in the ED Diagnosed with pneumonia by hospitalist faculty and treated with antibiotics Chronic illness: Cardiac, pulmonary, neurologic, chromosomal, craniofacial Setting: Single Children's hospital, 4/2011-3/2015
EXPOSURE	Candidate Risk Factors Included: Demographic: Age, sex, insurance, race/ethnicity History: Prematurity, prior ICU or respiratory admission, 1° relative with asthma Clinical: Weight per age (Z score), peak respiratory rate in the ED On ED presentation: Hypoxemia (< 90%) or accessory muscle use/retractions
NO EXPOSURE	Absence of risk factors above
OUTCOME	Respiratory decompensation with addition of ventilatory support: High-flow nasal cannula, continuous positive airway pressure, nasal intermittent mandatory ventilation, bi-level positive airway pressure, or intubation
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	Yes (Table 1). Patients had a diverse range of demographic characteristics including gender, age, race, prematurity, and prior respiratory admissions. Minorities were heavily represented. Patients were also categorized (Table 3) according to presence in the ED of hypoxemia, respiratory distress, tachypnea, and family history of asthma, but tachypnea is the only variable which is similar in patients with and without respiratory failure.
Were the circumstances and methods for detecting the outcome similar?	Yes. The outcome is respiratory decompensation as evidenced by the addition of ventilatory support. This included the need for high-flow nasal cannula, continuous positive airway pressure, nasal intermittent mandatory ventilation, bi-level positive airway pressure, or intubation. However, the threshold for initiating these is not described and is likely physician-dependent, since data was collected from the EMR. A second reviewer assessed 10% of the charts for accuracy.
Was follow-up sufficiently complete?	Yes. Follow up was complete, in the sense that patients were admitted to the floor and observed to determine respiratory status until decompensation or discharge. Therefore, patients were not discharged before the presence or absence of respiratory decompensation could be determined.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

Demographic Data (Tables 1, 2):
N = 1,217, median age 6.9 months, IQR (2.7, 12.9), female 41.1%, premature 18%,
Medicaid 82.1%, Race/Ethnicity: Hispanic 48.6%, Black 20.8%, White 4.6%, Other/unknown 26%
Decompensation: 121/1,217 = 9.9%, 95% CI (8.4, 11.8%)
Ventilation: HFNC 73%, CPAP 9%, NIMV 15%, BiPAP 3%, Intubation 1%, (99.2% non-invasive – 120/121 patients)

Bivariable Analysis (Table 3):
Young age, black race, hypoxemia, peak respiratory rate, and retractions/accessory muscle use (respiratory distress) were statistically significantly associated with decompensation requiring ventilation

MULTIVARIABLE ANALYSIS: INDEPENDENT PREDICTORS OF DECOMPENSATION

Predictors (Table 4)	Adjusted Odds Ratio	95% CI	Beta Coefficient
Age ≤ 3 months*	3.25	2.09, 5.07	1.18
Age 3-6 months*	1.76	1.04, 3.00	0.57
Black Race**	1.94	1.27, 2.95	0.66
Hypoxemia (< 90%)***	2.34	1.30, 4.21	0.85
Accessory muscle use	2.26	1.48, 3.46	0.82

*Compared to reference standard of 6-24 months
**Compared to reference standard of non-black race
***Compared to the absence of the predictor. Predictors defined as at ED presentation

Bronchiolitis Risk Score (Supplemental Materials)

Bronchiolitis Risk Score = (Age ≤ 3 months X 1.18) + (Age 3–6 months X 0.57) + (Black Race X 0.66) + (Hypoxia in ED X 0.85) + (Retractions/Accessory muscle use in ED X 0.82)
(Insert a zero (0) in the equation if the factor is absent and a one (1) if the factor is present.

Median score 1.18. Each increase in the score by 1 is associated with 2.7 times increased odds of respiratory decompensation.

The beta coefficients range from 0.57 to 1.18. The beta coefficient is a unit less measure that can be compared between predictors. For example, Age < 3 months (beta = 1.18) is approximately twice (1.18/0.57 = 2.1) as predictive of decompensation as an age of 3-6 months (beta = 0.57).
C statistic (analogous to the AUC) = 0.7 for predicting respiratory decompensation.
Generally interpreted as: 0.5-0.7 (weak), 0.7-0.8 (good), > 0.8 (very good).

		DECOMPENSATION		
		YES	NO	
RISK FACTORS	≥ 1 Factor (1-5)	115	912	1,027
	< 1 Factor (0)	6	184	190
		121	1,096	1,217

TEST CHARACTERISTIC	CALCULATION	ESTIMATE 95% CI
Prevalence	121/1,217	9.9% (8.4, 11.8%)
Sensitivity	115/121	95% (89.6, 97.7%)
Specificity	184/1,096	16.8% (14.7, 19.1%)
Predictive Value of a Positive Test	115/1,027	11.2% (9.4, 13.3%)
Predictive Value of a Negative Test	184/190	96.8% (93.3, 98.5%)
Livelihood Ratio of a Positive Test	(115/121)/(912/1,096)	1.14 (1.08, 1.19)
Likelihood Ratio of a Negative Test	(6/121)/(184/1,096)	0.30 (0.13, 0.65)

Essentially, the presence of 1 or more risk factors stratified a population with a 9.9% risk of respiratory decompensation into a high risk group (PV(+) = 11.2%) if 1 or more predictors were presents and a low risk group (1-PV(-) = 100 – 96.8% = 3.2%) if zero predictors were present.

HOW PRECISE IS THE ESTIMATE OF THE RISK?
Confidence intervals for the adjusted odds ratio and test characteristics are presented above

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Yes. The study patients were relatively similar since they encompassed many ethnicities and gestational ages. However, since patients with comorbidities were not included and non-minority patients were at a minimum the study's results may not be applicable to them.
Was follow-up sufficiently long?	Yes. Follow up was long since patients were followed while inpatient to determine presence or absence of respiratory decompensation. However, since the study was observational in nature, there were certain limitations regarding follow up, including inability to determine day of illness, unknown prior exposures such as second-hand smoking, and lack of time-to-event analysis (i.e. time from inpatient admission to respiratory decompensation).
Is the exposure similar to what might occur in my patient?	Yes. ED variables including hypoxemia and retractions/ accessory muscle use on presentation were observed to be predictors of respiratory decompensation, and these are exposures we will definitely see in our patients in the ED. Additionally, age (<6 months) and race (black race) are other exposure factors which were noted to be associated with respiratory decompensation. However, 26% of patients coded as 'other/unknown' for race. Additionally, many preterm infants were not included since all patients with comorbidities (i.e. CLD) were excluded from the study. Our population similarly has many preterm infants with comorbidities for whom this study would not be applicable.
What is the magnitude of the risk?	The beta coefficients for the 5 independent predictors of decompensation range from 0.57-1.18 and are provided in the results section. The C statistic was 0.7 indicating a weak to good predictive ability of the model.
Are there any benefits that offset the risks associated with exposure?	There are no known benefits of the variables (young age <6 months, black race, hypoxemia in the ED, retractions or accessory muscle use in the ED) that offset the risk of respiratory decompensation.

CLINICAL BOTTOM LINE

BACKGROUND: Viral bronchiolitis is an acute infectious inflammatory condition of the airways, which causes significant respiratory distress in infants and young children. Although most children require only supportive care, approximately 2-7% decompensate requiring ventilatory support. Identification of risk factors for decompensation would enable clinicians to selectively determine which children are at higher risk and may benefit from expectant monitoring or perhaps admission to a higher level of care. Children who are lower risk would not benefit from additional surveillance. This study sought to identify predictors of respiratory decompensation among otherwise healthy children with bronchiolitis admitted to the general floor. The study postulates that demographic and clinical factors identifiable on presentation to the emergency department (ED) can be used to identify those at risk for subsequent decompensation and need for ventilatory support.

CLINICAL QUESTION: In otherwise healthy infants and toddlers less than 24 months of age admitted to the general inpatient unit with a diagnosis of bronchiolitis, are there demographic and clinical factors identifiable in the emergency department associated with decompensation requiring ventilatory support?

DESIGN/RISK OF BIAS: This was a fairly well-designed study with a moderate risk of bias. The study is a retrospective cohort study at a single institution that included 1,217 patients in the analysis. Included patients were less than 24 months of age with a primary or secondary diagnosis of bronchiolitis who were admitted to an inpatient unit through the ED. Patients were excluded if ventilatory support was required in the ED, or if they were diagnosed and treated for pneumonia or had a chronic illness. Demographic, history, and clinical variables were assessed as potential predictors. The primary outcome event was respiratory decompensation requiring the addition of ventilatory support including high-flow nasal cannula, continuous positive airway pressure, nasal intermittent mandatory ventilation, bi-level positive airway pressure, or intubation as documented in the medical record.

There are limitations due to the study's observational nature, including inability to determine time from illness onset, prior exposures such as second-hand smoking, and unknown time-to-event analysis (i.e. time from inpatient admission to respiratory decompensation).

PRIMARY RESULTS: Decompensation requiring ventilatory support occurred in 9.9%, 95% CI (8.4, 11.8%) of patients. 99.2% of the time this consisted of non-invasive ventilation techniques. Logistic regression identified 5 independent predictors of respiratory decompensation. Patients without any of the risk factors had a 3% risk of decompensation. However, only 15.6% of patients had none of the risk factors. Those with at least one of the risk factors had an 11.2% risk of decompensation which is not markedly different from the baseline 9.9% risk of decompensation in the population as a whole. Two of the predictors, hypoxia and accessory muscle use, were based on ED presentation. It may have been helpful to analyze these predictors at the time that a disposition decision was made, though this was likely not available retrospectively.

MULTIVARIABLE ANALYSIS: INDEPENDENT PREDICTORS OF DECOMPENSATION			
Predictor	Adjusted Odds Ratio	95% CI	Beta Coefficient
Age ≤ 3 months*	3.25	2.09, 5.07	1.18
Age 3-6 months*	1.75	1.04, 3.00	0.57
Black Race**	1.94	1.27, 2.95	0.66
Hypoxemia (< 90%)***	2.34	1.30, 4.21	0.85
Accessory muscle use	2.26	1.48, 3.46	0.82
*Compared to reference standard of 6-24 months **Compared to reference standard of non-black race ***Compared to the absence of the predictor. Predictors defined as at ED presentation			

The supplemental materials include a description of a Bronchiolitis Risk Score. The beta coefficients range from 0.57 to 1.18. Each increase in the Bronchiolitis Risk Score by 1 is associated with 2.7 times increase in the odds of respiratory decompensation. The c-statistic of 0.7 indicates a weak to good predictive ability of the variable model. While a c-statistic was presented it would have been helpful to present a receiver operating characteristic curve.

APPLICABILITY: This single institution study's results may not be generalizable to other institutions. Criteria for requiring ventilation were not provided and was likely at the treating clinician's discretion. It is also unclear if this decision was made by hospitalist faculty. Additionally, initial criteria for admission from the ED to the ICU were not presented.

The study population was heavily weighted toward minorities (69.4% Hispanic or Black). By design the study excluded those with comorbid conditions but included premature infants without comorbid conditions. 15.5% of screened patients were excluded for comorbidities. Prematurity was not found to be associated with respiratory decompensation, but this is likely because the study does not include preterm infants with comorbidities.

AUTHOR'S CONCLUSION: "We found that age < 6 months, black race, hypoxemia in the ED, and retractions or accessory muscle use on ED physical examination are independent predictors of respiratory decompensation after admission among otherwise healthy children with bronchiolitis admitted initially to the general floor. We believe that these factors should be considered by clinicians in determining which children selectively require a higher level of monitoring or require transfer to another institution if the appropriate monitored setting is not available or if the capability to provide ventilatory support is limited."

POTENTIAL IMPACT: This study could be applied to a setting very similar to its own (i.e. predominantly minority population, preterm infants without comorbidities), but due to its various limitations, it is hard to generalize the results to other clinical settings and other patient populations. While the above risk factors may be associated with respiratory decompensation in bronchiolitis, more research is needed before the results can be widely applied. Importantly, approximately 10% of patients decompensated with all but one patients requiring non-invasive ventilation. This highlights the need to closely observe these patients.

BRONCHIOLITIS:
EPINEPHRINE DOSING SCHEDULE

In children, less than 12 months who are admitted for moderate to severe bronchiolitis, is nebulized Racemic Epinephrine when compared to Placebo (Saline) administered on a Fixed schedule when compared to an On-demand schedule associated with a shorter length of hospital stay?

Joshua Beiner, M.D., Michael Mojica, M.D.
November, 2013

Skjerven HO, Hunderi JO, Brügmann-Pieper SK, Brun AC, Engen H, Eskedal L, Haavaldsen M, Kvenshagen B, Lunde J, Rolfsjord LB, Siva C, Vikin T, Mowinckel P, Carlsen KH, Lødrup Carlsen KC.

RACEMIC EPINEPHRINE AND INHALATION STRATEGIES IN ACUTE BRONCHIOLITIS

N Engl J Med. 2013 Jun 13;368(24):2286-93,
PubMed ID: 23758233

STUDY DEFINITIONS	
POPULATION	Inclusion: < 12 months, clinical signs of bronchiolitis (See Appendix), admitted, clinical score ≥ 4/10 (See Appendix). Exclusion: Any serious cardiac, immunologic, neurologic, oncologic disease or pulmonary disease (other than bronchiolitis), > 1 previous episode of obstructive airway disease. lower airway symptoms (e.g., coughing) for > 4 weeks, glucocorticoids within 4 weeks. Setting: 8 Centers (Norway), 1/2010-5/2011
CONTROL INTERVENTIONS	Medication: Racemic Epinephrine or Placebo (Saline) Administration Schedule: On Demand or on a Fixed schedule (up to Q2 Hours)
	Dosing: < 5kg = 0.10 ml, 5-6.9kg = 0.15 ml, 7-9.9kg = 0.20 ml, > 10kg = 0.25 ml Diluted with 2 ml saline, administered by nebulizer with 100% O_2 at 6 liters/min Racemic Epinephrine: 20 mg/ml Placebo: 0.9% Saline Corticosteroids and beta agonists were not administered
OUTCOME	Primary Outcome: Length of hospital stay (Time from 1st treatment to discharge) Secondary Outcomes: Change in clinical score 30 minutes after 1st treatment Supportive Therapies: Use of supplemental oxygen Nasogastric tube feeding Ventilatory support
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized in computer-generated blocks of 8 with assignments to 1 of 4 treatment groups.
Was randomization concealed?	Yes. The study centers were unaware of randomization block size and were provided with a list of study numbers to use in consecutive assignment of study medications. Randomization codes were communicated directly from the study statistician to study pharmacist. There does not appear to be opportunity to bias allocation though it is not specifically mentioned by the authors.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Patients met similar inclusion criteria including definition of illness, age, and minimum clinical scores while excluding those with chronic or recurrent disease, possible confounding comorbidities, or recent use of glucocorticoids. No. Several characteristics, including medical history and parental medical history appear to have large between-group differences.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study was double-blinded. The study pharmacist coded study medication for type of medication and timing of administration. Additional saline nebulizers treatments or other supportive care measures could be ordered by the attending regardless of study group.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	No. 14% of did not complete the study interventions (Figure 1), 71% of these were due to treatment failure. Rescue medications given or critical interventions made (e.g., PICU admission, BiPAP) were not presented for these patients.
Were patients analyzed in the groups to which they were randomized?	An Intention to Treat (ITT) analysis was performed in patients with sufficient data. A Per Protocol analysis, included in the supplement, demonstrated no difference due to medication given and a similar benefit to the ITT analysis for administration on a demand basis.
Was the trial stopped early?	No. The trial was not stopped early. 352 patients were required by the sample size determination and 404 were included.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 404 infants, mean age 4.2 months
Average clinical score: 4.9/10

FIGURE 1		RANDOMIZED	COMPLETED
Epinephrine	On Demand	102	85 (83%)
Epinephrine	Fixed	101	82 (81%)
Placebo	On Demand	98	78 (80%)
Placebo	Fixed	103	76 (75%)
	TOTALS	404	348 (86%)

Length of Stay (Medications)
Estimated Mean in hours with 95% CI
Saline: 68.1 hours (49.8, 86.4 hours)
Racemic Epinephrine: 63.6 hours (46.2, 81.0 hours)
Difference (Saline – RE) = 4.5 hours (-6.5, 15.5)

No difference in: Nasogastric feeds, O_2 supplementation or ventilatory support

Length of Stay (Delivery Schedule)
Estimated Mean in hours with 95% CI
Fixed-Schedule: 61.3 hours (45.4, 77.2)
On-Demand: 73.9 hours (64.6-83.2)
Difference (Fixed - Demand) = 13.7 hours (2.9, 24.4)

The authorized specified a 5-hour difference in length of stay to be clinically significant in their sample size determination.

Significantly more supplemental oxygen (48.7% vs 38.3%) and ventilator support (10.8% vs 4.0%) in the Fixed Schedule groups. No difference in nasogastric feedings.

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See confidence intervals for the time differences above. The confidence intervals for the mean differences are wide (imprecise).

Statistically significant difference in Estimated LOS > 5 hours between On-Demand and Fixed groups persisted in supplemental subgroup analysis in the ‘No Previous Wheeze’ and ‘Age < 3 months’ groups.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Unlikely. The patient population was a predominantly Caucasian Scandinavian population. Atopic disease in this study appears lower than is typical of our NYC urban population. In contrast to many studies, patient with a single episode of a previous episode of airway obstruction were not excluded. The dose of Racemic Epinephrine, though standard in the study's setting, was approximately 40% of the dose commonly given in the US. This may have biased against the Epinephrine group.
Were all patient important outcomes considered?	Data was not available in 83 patients on the initially intended primary outcome of "the time at which the child was deemed ready for discharge" so the actual time to discharge was utilized. It is questionable if a 5 hour shorter hospital LOS represents a clinically significance difference, especially when LOS was based on leaving the inpatient service rather than the patient meeting standardized discharge criteria.
Are the likely treatment benefits worth the potential harm and costs?	Unclear. The significantly lower dose of Epinephrine used may underestimate the effective or Epinephrine but also underestimate potential adverse events.

CLINICAL BOTTOM LINE

BACKGROUND: In most healthy infants, bronchiolitis is a self-limited condition and treatment strategies involve techniques to maintain oxygenation and hydration. When more severe disease requires admission, current practice guidelines recommend primarily supportive care, including supplemental oxygen, suctioning, and intravenous fluids. Guidelines do not recommend a trial of beta agonists. However, one of difficulties is distinguishing the majority of patients with primary bronchiolitis from the few who may have a virally-induced bronchospasm component. Beta agonists are frequently trialed in the hope that patients with a history of atopy or a family history of asthma will respond. Epinephrine is both a beta and alpha agonist. The addition of alpha activity may reduce airway edema through vasoconstriction even if a beta agonist is ineffective.

CLINICAL QUESTION: In children, less than 12 months who are admitted for moderate to severe bronchiolitis, is nebulized Racemic Epinephrine when compared to Placebo (saline) administered on a Fixed schedule when compared to an On-demand schedule associated with a shorter length of hospital stay?

DESIGN/VALIDITY: This was a well-designed study comparing nebulized racemic Epinephrine to Saline and On-Demand dosing to a Fixed-Schedule regimen. Patients could not receive corticosteroids or beta agonists as co-interventions. There are some validity concerns including not standardizing Emergency department interventions prior to randomization and choosing a primary outcome with questionable clinical significance (i.e., difference in length of hospital stay of > 5 hours). The study utilized approximately 40% of the Racemic Epinephrine dose used in the US potentially underestimated the effectiveness of racemic epinephrine but also underrepresenting its potential adverse events compared to US dosing.

PRIMARY RESULTS: The primary results of the study are presented in Table 2. It is important to understand the study groups as presented in the table. For example, the inhaled Racemic Epinephrine group represents Epinephrine patients in both the On-demand and Fixed regimens. Similarly, the On-demand group includes both patients who received Epinephrine and those who received Placebo (Saline).

STUDY RESULTS BY RANDOMIZATION GROUPS (FROM SUPPLEMENT)

	Adrenaline On-Demand N = 102	Saline On-Demand N = 98	Adrenaline Fixed N = 101	Saline Fixed N = 103
Length of Stay (hrs)	71.6	76.3	85.9	87.0
Δ Clinical Score	-1.22	-1.15	-1.31	-1.01
Oxygen	38.5%	38.0%	47.9%	49.5%
NG Tube Feeds	27.7%	24.7%	29.0%	34.3%
Ventilatory Support	2.0%	6.1%	12.9%	8.7%

There were no significant differences in length of stay, supportive therapies, or treatment discontinuation between the Racemic Epinephrine and Saline groups. There were significant differences in the On-Demand vs Fixed-Schedule groups. The On-Demand groups remained admitted on average 13.7 hours less than Fixed-Schedule groups. The On-Demand group required less supplemental oxygen and ventilator support. Of note, the Fixed-Schedule groups received, on average, 5 additional nebulizer treatments during their hospitalization (12 vs 17 treatments). This higher number of treatments rather than a diminished protocol effectiveness may contribute to the longer hospital course.

APPLICABILITY: The study's result can likely be generalized to infants with moderate to severe bronchiolitis meeting the study's inclusion and exclusion criteria. It is unclear however if a Norwegian bronchiolitis population differs significantly from a US populations. In contrast to many studies, patients with a single episode of a previous episode of airway obstruction were not excluded. This could likely make the results applicable to patients in which there is concern for a bronchospastic component.

AUTHOR'S CONCLUSION: "In conclusion, our study showed that for hospitalized infants with acute bronchiolitis, inhaled racemic Epinephrine was not superior to inhaled saline with regard to length of hospital stay, use of supportive treatment, or clinical score. However, the administration of inhalations on demand, as compared with a fixed schedule of inhalations, was associated with a shorter hospital stay and with a reduced need for supportive treatment."

POTENTIAL IMPACT: Current guidelines do not recommendation inhaled bronchodilators for acute bronchiolitis. This study did not find a benefit in length of stay, clinical score or additional interventions in those administered Racemic Epinephrine compared to Saline via nebulizer. On-demand administration was associated with a shorter length of stay, less supplemental oxygen and less need for ventilatory support than a fixed administration schedule.

APPENDIX

BRONCHIOLITIS DEFINITION: “Illness mainly affecting infants, especially in the first 6 months of life. Rapid respiration, dyspnea, wheezing, chest recession, cough, rhonchi and rales are very frequent. Visible distension of the chest and increased pulmonary translucency on the chest radiograph are frequent and of high diagnostic significance. Upper respiratory features, especially nasal discharge and a red pharynx are frequent. Fever is very frequent, but high fever is uncommon.” (Very frequent is ≥ 50%, Frequent is 25-50% of children)

CLINICAL SCORE			
	SCORE 0 (Normal)	SCORE 1 (Mild-Moderate)	SCORE 2 (Severe)
Respiratory Rate (Breaths/minute)	< 40	40-60	> 60
Respiratory Chest Recessions	None	Moderate Costodiaphragmatic	Severe As 1, plus rib and jugular retraction
Auscultatory Breath Sounds	Vesicular	Wheeze + Rales/ Rhonchi	Faint ± severe wheeze ± pronounced rales and rhonchi
Skin Colour	Normal	Pallor	Cyanosis
General Condition	Not affected	Moderately affected	Severely affected
The score of each of the 5 sub-scores are added to get a total score with a range of 0-10			

BRONCHIOLITIS:
HIGH FLOW OXYGEN VIA NASAL CANNULA

In infants less than 12 months of age presenting to the ED or inpatient unit with a clinical diagnosis of bronchiolitis requiring supplemental oxygen, does High Flow Nasal Cannula (HFNC) with supplemental oxygen when compared to standard therapy (ST) with supplemental oxygen alone, decrease treatment failures requiring an escalation of care?

John Park, M.D., Michael Mojica, M.D.
May 2018

Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J, Furyk J, Fraser JF, Jones M, Whitty JA, Dalziel SR, Schibler A.

A RANDOMIZED TRIAL OF HIGH-FLOW OXYGEN THERAPY IN INFANTS WITH BRONCHIOLITIS

N Engl J Med. 2018 Mar 22;378(12):1121-1131.
PubMed ID: 29562151

STUDY DEFINITIONS	
POPULATION	Inclusion: < 12 months, present to ED or inpatient unit with: Clinical signs of bronchiolitis (defined by AAP as symptoms of respiratory distress associated with symptoms of a viral respiratory tract infection) and the need for supplemental O_2 to keep the O_2 saturation at 92-98% (n=6 institutions) or 94-98% (n=11 institutions) Exclusion: Critically ill infants (need for respiratory support and ICU admit) Cyanotic heart disease Basal skull fracture Upper airway obstruction Craniofacial malformation Receiving home oxygen therapy Setting: n=17 tertiary and regional hospitals (Australia, New Zealand) 10/2013-8/2016
INTERVENTION	High Flow Nasal Canula Group (HFNC): Heated/Humidified O_2 at 2 liters/kg/minute Supplemental O_2 to keep the O_2 saturation at 92-98% (n=6 institutions) or 94-98% (n=11 institutions) High-flow oxygen therapy was stopped after 4 hours of receiving an Fio2 of 21% (room air) while oxygen saturation was maintained in the expected range
CONTROL	Standard Therapy Group (ST): Supplemental O_2 at a maximum of 2 liters/minute, Supplemental O_2 to keep the O_2 saturation at 92-98% (n=6 institutions) or 94-98% (n=11 institutions)
CO-INTERVENTION	Weaning of the FiO_2 to ambient air permitted at any time to provide the lowest possible FiO_2 to maintain O_2 saturation ≥ 92% or ≥ 94% depending on institution Enteral feeding recommended Additional therapy at treating MD discretion
OUTCOME	Primary Outcome: Treatment Failure requiring Escalation of Care Treatment Failure: Required ≥ 3 of 4 criteria or at physician discretion 1. Heart rate: Increased or No decrease 2. Respiratory rate: Increased or No decrease 3. Oxygen required > 40% (HFNC group) or > 2 liters/minute (ST group) 4. Hospital early warning tool triggered: A combination of physiologic and clinical variables. Identical at 11 institutions, comparable at other 6 institutions Escalation of Care: Need for increased respiratory support or transfer to the ICU Secondary Outcomes: 1. Proportion admit to ICU 2. Length of stay: Inpatient and ICU (if needed) 3. Duration of oxygen therapy 4. Intubation 5. Adverse events Subgroups (pre-planned analyses): 1. Premature (< 37 weeks) 2. Prior hospital admission for a respiratory disease 3. Age: < 3 months and < 6 months (corrected for prematurity) 4. Congenital heart defect 5. On site presence of ICU or transfer required to outside ICI
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes: A computer-generated randomization sequence with a block size of 10 was used, and infants were stratified according to participating center.
Was randomization concealed?	No. Masking of the assigned treatment was not possible, given the visually obvious difference between the two interventions. Sequentially numbered, sealed, opaque envelopes containing the treatment assignment (in a 1:1 ratio) were opened when eligibility criteria were met.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. (Table 1) 31% in the standard group and 25% in the HFNC group had a prior admission for respiratory disease. This seems particularly high. In addition, there was no measure of disease severity comparing the two groups. Either a validated respiratory score or respiratory rate and work of breathing could have been included.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study was not blinded. Masking of the assigned treatment was not possible, given the visually obvious difference between the two interventions.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Measured outcomes all occurred during the hospital stay. However, there was no follow up after the patients were discharged from the hospital. It would have been helpful to present unscheduled return visits and in particular return visits requiring additional interventions or admission.
Were patients analyzed in the groups to which they were randomized?	Yes. This was an intention to treat analysis. The authors state that “the primary and secondary outcomes were analyzed on the basis of the assigned treatment group” In figure 1, 733 patients were randomized and allocated to the standard group and 739 patients to the HFNC group. In table 2 (primary outcomes and subgroups) and table 3 (secondary outcomes), all of the those who were randomized and allocated were included in the analyses. There were 167 patients in the ST group that received rescue HFNC after failing treatment. They were analyzed with the ST group.
Was the trial stopped early?	No. The trial was not stopped early. The sample size determination required 1,400 patients and 1,472 were included in the analyses.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 1,472 (HFNC = 739, Standard = 733)
Time to escalation: HFNC: 17.3 ± 19.7 hours, Standard: 16.1 ± 19.9 hours
Treatment failure: 254/1,472 = 17%
Escalation: Primary reason = Hospital warning score triggered,
Treatment Failure not meeting ≥ 3 or 4 criteria for treatment failure (i.e. at MD discretion): 34%
Standard group escalations: 100% started on HFNC, 61% response to rescue HFNC.

Primary Outcome: Treatment Failure with Care Escalation

	TREATMENT FAILURE WITH CARE ESCALATION		
	YES	NO	
HFNC GROUP	87	652	739
ST GROUP	167	566	733

Absolute Risk (HFNC): 87/739 = 12%
Absolute Risk (ST): 167/733 = 23%
Absolute Risk Difference = AR (ST) – AR (HFNC) = 23% - 12% = 11%, 95% CI (7, 15%)
(The authors considered a 5% reduction to be clinically significant in their power analysis)
Relative Risk = AR (HFNC) / AR (ST) = 12%/23% = 0.52, 95% CI (0.40, 0.66)

Subgroup Analysis: Treatment Failure with Care Escalation for preplanned subgroups
There was no statistically significant difference in the primary outcome for: Age categories (< 3 months, < 6 months, 6 months – 1 year), prematurity, RSV status or independently confirmed to have ≥ 3 or 4 criteria for treatment failure. There was a statistically significant difference in the primary outcome for: Hospital with an in-house ICU (ARD = 6%, 95% CI (1, 11%)) compared to without an in-house ICU (ARD = 21%, 95% CI (14, 27%).

Secondary Outcomes:
No statistical difference in LOS, PICU LOS or duration of oxygen therapy
12 intubations (0.8%) (HFNC 8, Standard 4)
Adverse events: N=2 pneumothorax (1 in each group), N=6 apnea (3 in each group)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See confidence intervals for risk differences and relative risk above

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. This was a multicenter study. The trial was done in Australia and New Zealand so the demographics of the patient population may be different from our population. In addition, these were patients with a high rate of prior respiratory admissions (HFNC 25%, Standard 31%). A subgroup analysis of prior admission did not affect the primary outcome. Additional subgroup analyses showed no difference comparing hospitals with and without an ICU, patients age, prematurity or respiratory status
Were all patient important outcomes considered?	Yes. The study included the primary outcome and relevant subgroups as well as many secondary outcomes.
Are the likely treatment benefits worth the potential harm and costs?	Yes. HFNC is a minimally invasive treatment that can help prevent the need for ICU admission when delivered outside of the ICU. NNT = 1/0.11 = 9, 95% CI (7, 14). For every 9 patients treated with HFNC 1 additional patient did not have a treatment failure.

CLINICAL BOTTOM LINE

BACKGROUND: There has been an increase in use of high-flow warm, humidified oxygen via nasal cannula (HFNC) in patients with bronchiolitis despite limited evidence. The preponderance of the evidence has been from small case series. In theory, the function of HFNC is similar to positive end expiratory pressure in that airway pressure would increase the effective alveolar surface area and improve ventilation/perfusion mismatch. A recent, randomized trial including 202 patients less than 2 years of age with moderate bronchiolitis did not find a statistically difference in the primary outcome of time to weaning of oxygen for HFNC compared to standard therapy. However, there was a significant reduction in the proportion with treatment failure within the first 24 hours (Risk Difference: 19%, 95% CI (8, 30%). In addition, 2/3 of patients who deteriorated on standard therapy were able to be rescued with HFWHO (Kepreotes, Lancet. 2017, PubMed ID: 28161016).

CLINICAL QUESTION: In infants less than 12 months of age presenting to the ED or inpatient unit with a clinical diagnosis of bronchiolitis requiring supplemental oxygen, does High Flow Nasal Canula (HFNC) with supplemental oxygen when compared to standard therapy (ST) with supplemental oxygen alone, decrease treatment failures requiring an escalation of care?

DESIGN/VALIDITY: This was a well-design, multicenter randomized clinical trial that included 1,472 patients in the primary intentional to treat analysis. The study took place at 17 tertiary care and regional hospitals in Australia and New Zealand. The trial was not blinded as there were obvious differences between equipment used for HFNC vs standard therapy. Infants in the standard therapy group could be escalated HFNC as rescue for treatment failure.

Treatment failure was defined as at least three of four clinical criteria being met or clinicians deciding that escalation of care was required. The criteria were as follows:
1. Heart rate: Increased or No decrease
2. Respiratory rate: Increased or No decrease
3. Oxygen required > 40% (HFNC group) or > 2 liters/minute (ST group)
4. Hospital early warning tool triggered: A combination of physiologic and clinical variables.

Enrollment was based on oxygen requirement. 2 recent studies have found that oxygen should not be used as a primary determinant of bronchiolitis management. (Schuh, JAMA. 2014, PubMed ID: 25138332, Principi, JAMA Pediatr. 2016 PubMed ID: 26928704). There was no characterization of the work of breathing. There was no follow up after the patients were discharged from the hospital. It would have been helpful to present unscheduled return visits and in particular return visits requiring additional interventions or admission.

PRIMARY RESULTS: The time to escalation in HFNC group was 17.3 ± 19.7 hours and in the ST group was 16.1 ± 19.9 hours. The primary indication for escalation was triggering of the hospital warning score triggered. 34% of escalations were at treating physician discretion and did not meet ≥ 3 or 4 criteria for treatment failure. A subgroup analysis based on escalation criteria did not reveal a difference in the primary outcome.

Treatment failure occurred in 17% (254/1,472) of patients, 12% in the HFNC group an 23% in the ST group (Risk difference: 11%, 95% CI (7, 15%). The authors considered a 5% reduction to be clinically significant in their power analysis. The 11% difference represents both a statistically and clinically lower in the HFNC group by the author's criteria. 100% of the escalations in the ST group were started on HFNC and 61% responded.

In preplanned subgroup analyses there was no statistically significant difference in the primary outcome for: age categories (< 3 months, < 6 months, 6 months-1 year), prematurity, RSV status or independently confirmed to have ≥ 3 or 4 criteria for treatment failure. The was a statistically significant difference in the primary outcome for: hospital with an in-house ICU (ARD = 6%, 95% CI (1, 11%)) compared to without an in-house ICU (ARD = 21%, 95% CI (14, 27%).

Of the secondary outcomes, there was no statistical difference in inpatient or PICU length of stay or duration of oxygen therapy. There were 12 intubations (HFNC 8, Standard 4) and no serious adverse events. Two patients developed a pneumothorax (1 in each group) and 6 developed apnea (3 in each group)

APPLICABILITY: This was a multicenter study conducted at 17 tertiary care and regional hospitals in Australia and New Zealand so the demographics of the patient population may be different from our population. In addition, these were patients with a high rate of prior respiratory admissions (HFNC 25%, Standard 31%). A subgroup analysis of prior admission did not affect the primary outcome. Additional subgroup analyses showed no difference comparing hospitals with and without an ICU, patients age, prematurity or respiratory status. The study's results are likely generalizable to patient's meeting the enrollment criteria.

AUTHOR'S CONCLUSION: "In conclusion, our randomized, controlled trial involving infants with bronchiolitis showed a significantly lower rate of escalation of care due to treatment failure when high-flow oxygen therapy was used early during the hospital admission than when standard oxygen therapy was used."

POTENTIAL IMPACT: HFNC is a minimally invasive treatment that can help prevent the need for ICU admission when delivered outside of the ICU. The number need to treat was 9, 95% CI (7, 14) (NNT = 1/ARD = 1/0.11). For every 9 patients treated with HFNC 1 additional patient did not have a treatment failure. There were no adverse events associated with HFNC. In addition, 63% of the patients in the ST group that had a treatment failure benefited from HFNC. An important next step would be to identify those patients at higher risk of treatment failure.

BRONCHIOLITIS:
HOME OXYGEN DESATURATION

In pediatric patients with bronchiolitis who are discharged from the emergency department with a home oxygen saturation monitor (with the display and alarms turned off) are oxygen desaturations associated with unscheduled return visits?

Michael Mojica, M.D.
August 30, 2016

Principi T, Coates AL, Parkin PC,
Stephens D, DaSilva Z, Schuh S.

EFFECT OF OXYGEN DESATURATIONS ON SUBSEQUENT MEDICAL VISITS IN INFANTS DISCHARGED FROM THE EMERGENCY DEPARTMENT WITH BRONCHIOLITIS.

JAMA Pediatr. 2016 Jun 1;170(6):602-8.
PubMed ID: 26928704

STUDY DEFINITIONS	
POPULATION	Inclusion: Previously healthy, 6 weeks–12 months with a clinical diagnosis of bronchiolitis (1st episode of respiratory distress with cough, coryza, wheezes or crackles and tachypnea or chest retractions) Exclusion: Anomalies of the cardiopulmonary, neuromuscular, immunologic, hematologic or airway systems, < 36 weeks' gestation, chronic hypoxia, those requiring admission and poor command of English Setting: Single Children's Hospital ED. 2/2008-4/2013
STUDY PROCEDURES	Structured data collection form: Diary of sleeping, feeding, sitting in car seat Portable O_2 monitor with threshold alarms and display turned off, only alarm for probe displacement. Artifacts, poor signals excluded from analysis. Mean 20 hours Phone follow-up at 72 hours (blinded to presence/absence of desaturation)
EXPOSURE	Those with desaturation to < 90% for ≥ 1 minute
NO EXPOSURE	Those without desaturation to < 90% for ≥ 1 minute
OUTCOME	Primary: Unscheduled return visits (to any healthcare provider) for respiratory symptoms within 72 hours of ED discharge Secondary: Desaturation frequency, duration. Activity during desaturations. Major desaturations: Recurrent = ≥ 3 desaturations < 90% for > 1 minutes, Prolonged = desaturation < 90% for ≥ 10% of monitored time, Sustained = desaturation < 90% for ≥ 3 minutes Unscheduled return visits for any reason (all-cause) Unscheduled return visits: Major desaturations vs. no desaturation Delayed hospitalization Predictors of desaturation (regression analysis)
DESIGN	Observational: Prospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
Aside from the exposure of interest did the exposed and control groups start and finish with the same risk for the outcome?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or did statistical adjustments address the imbalance).	Yes. See Table 1. Those with and without desaturations were similar with regard to prognostic factors with the exception that those with desaturation had a higher rate of prior visits (70% vs 49%)
Were the circumstances and methods for detecting the outcome similar?	Yes. Unscheduled return visits were assessed by a structured telephone interview. Outcome assessors were blinded to the presence or absence of desaturations.
Was follow-up sufficiently complete?	Yes. 10/139 (7%) patients were lost to follow-up

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

N = 118 patients
Desaturation: 75/118 (63.6%)

Primary Outcome: Unscheduled return visits for respiratory symptoms within 72 hours

		RETURN VISITS		
		YES	NO	
DESATURATIONS	YES	18	57	75
	NO	11	32	43

Absolute Risk (desaturation group) = 18/75 = 24%
Absolute Risk (no desaturation group) = 11/43 = 25.6%
Absolute Risk difference = AR (desat) – AR (no desat) = 24% - 25.6% = -1.6%.
There were 1.6% fewer return visits in the desaturation group. This difference was not statistically significant.

Secondary Outcomes:

Desaturations: 75/118 (64%). Of those with desaturation 79% with < 80% for > 1 minute and 39% with < 70% for > 1 minute. 77% of desaturations occurred during feeding or while sleeping.

Major Desaturations: 53%, 50% recurrent, 43% sustained and 10% prolonged.
No difference in return visits in those with (24%) or without (25%) major desaturations. Risk Difference: -0.8% (-0.16, 0.6)

All-cause return visits. Desaturation (32%) vs No Desaturation (37%). ARD 5.2% (-0.13, 0.23)

Hospitalizations: Desaturation (1%) vs No desaturation (5%). ARD -3.3% (-0.04, 0.10)

Regression analysis: Only previous medical visits was independently associated with desaturation.

HOW PRECISE IS THE ESTIMATE OF THE RISK?

The one sided 95% confidence interval for the absolute risk difference of -1.6% for the primary outcome is (-0.136 to infinity), (infinity due to a one-tailed hypothesis)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Unclear. 50% of patients received some treatment in the ED including 10% receiving corticosteroids. 1/3 of patients received a bronchodilator at discharge. 34% of the returning infants received additional medications. These treatments are not recommended by available evidence though a trial of bronchodilators may be warranted.
Was follow-up sufficiently long?	Unclear. Phone follow up occurred 3 days after discharge. Clinical deterioration after that time could have been missed. The mean duration of symptoms at presentation was 2 days and symptoms typically peak from 5-7 days. The majority of complications may have occurred by day five but a 5 day follow up period would have been optimal (to increase the duration since symptom onset to 7 days)
Is the exposure similar to what might occur in my patient?	Yes. There is no reason to suspect that the frequency of desaturation events would be less likely in our population
What is the magnitude of the risk?	Not applicable. There was not an increased risk of the outcome measure in those with desaturations.
Are there any benefits that offset the risks associated with exposure?	No. There are no known benefits of desaturations

CLINICAL BOTTOM LINE

BACKGROUND: Bronchiolitis is the most common lower respiratory tract infection and the most common cause of hospital admissions in infants. Admission decisions are typically based on the degree or respiratory distress, hydration status and need for supplemental oxygen. It is unclear if desaturation is associated with poor outcomes as it is often transient, and may not be associated with respiratory distress. The 2014, AAP Bronchiolitis practice guideline, recommends that a caregiver may choose not to administer oxygen for an oxygen saturation greater than 90%. Reliance on oxygen saturation may result in unnecessary admissions.

CLINICAL QUESTION: In pediatric patients with bronchiolitis who are discharged from the emergency department with a home oxygen saturation monitor (with the display and alarms turned off) are desaturations associated with unscheduled return visits?

DESIGN/VALIDITY: This was a well-designed prospective, cohort study conducted at a single Children's hospital. 118 patients (75 with desaturations and 43 without desaturations) were included in the analysis. Phone follow-up occurred at 3 days after ED discharge. Since patients presented on average with 2 days of symptoms the follow-up occurred at approximately 5 days since symptom onset. Since bronchiolitis symptoms peak on average from 5-7 days some later return revisits may have been missed. It is unclear why 50% of patients received some treatment in the ED including 10% receiving corticosteroids. 1/3 of patients received a bronchodilator on discharge. 10/29 (34%) of the returning infants received additional medications. These treatments are not recommended by available evidence though a trial of bronchodilators may be attempted.

PRIMARY OUTCOME: The majority (64%) of infants had desaturations to less than 90% for ≥ 1 minute (median duration 3.5 minutes). Of those with desaturations, 79% had a desaturation to < 80% for > 1 minute and 39% had a desaturation to < 70% for > 1 minute. 77% of desaturations occurred during feeding or while sleeping. Major desaturations occurred in 53% of infants. Of these infants 50% had recurrent desaturations (≥ 3 of < 90% for > 1 minute), 43% had sustained desaturations (< 90% for ≥ 3 minutes) and 10% had prolonged desaturations (< 90% for ≥ 10% of monitored time).

There was no difference in the rate of return visits; 18/75 (24%) in the desaturation group and 11/43 (25.6%) in the infants without desaturations (Absolute Risk Difference = - 1.6%, one sided 95% CI [-0.136 to infinity]. There was no difference in hospitalizations. There was no difference in return visits in those with and without major desaturations. In the regression analysis, only previous medical visits were independently associated with desaturation indicating the those with desaturation could not have been predicted at the time of ED discharge. A regression analysis with an outcome of unscheduled revisits was not presented.

Approximately 25% patients had an unscheduled revisit related to bronchiolitis and more than a 1/3 had an all-cause revisit. This seems particularly high. Perhaps a scheduled revisit at 48-72 hours to reassess the degree of hydration and respiratory distress and reassure caregivers would be warranted.

AUTHOR'S CONCLUSIONS: "The majority of infants with mild bronchiolitis experienced recurrent or sustained desaturations after discharge home. Children with and without desaturations had comparable rates of return for care, with no difference in unscheduled return medical visits and delayed hospitalizations. Pulse oximetry is not an effective tool to predict subsequent return for care."

POTENTIAL IMPACT: I would agree with the authors conclusions though a larger sample size and a longer follow-up interval would have increased my confidence in decreasing the reliance of oxygen saturation to determine the disposition of infants with bronchiolitis.

BRONCHIOLITIS:
HYPERTONIC SALINE AND EPINEPHRINE

In infants with mild to moderate bronchiolitis does 3% Hypertonic saline with Racemic epinephrine when compared to Normal saline and Racemic Epinephrine improve respiratory status and oxygen saturation at 2 hours in the emergency department?

Kelly Cleary, M.D., Sarah Case, M.D.

October 2010

Grewal S, Ali S, McConnell DW, Vandermeer B, Klassen TP.

A RANDOMIZED TRIAL OF NEBULIZED 3% HYPERTONIC SALINE WITH EPINEPHRINE IN THE TREATMENT OF ACUTE BRONCHIOLITIS IN THE EMERGENCY DEPARTMENT.

Arch Pediatr Adolesc Med. 2009 Nov;163(11):1007-12.,
PubMed ID: 19884591

STUDY DEFINITIONS	
POPULATION	Inclusion: 6 weeks-12 months, clinical diagnosis of mild to moderate bronchiolitis (first episode of wheezing and clinical symptoms of a viral respiratory infection), oxygen saturation ≥ 85% and ≤ 96%. Respiratory Distress Assessment Instrument (RDAI) score ≥ 4 Exclusion: Preexisting cardiac or pulmonary disease, previous diagnosis of asthma by a physician, any previous use of bronchodilators, severe disease requiring resuscitation room care, inability to take medication using a nebulizer, inability to obtain informed consent secondary to a language barrier, no phone access for follow-up. Setting: Single, Tertiary Care Children's Hospital ED (Canada). 2/2004-3/2005
INTERVENTION	3% Hypertonic saline 2.5 ml via nebulizer at 6 liters/minute
CONTROL	0.9% Normal saline 2.5 ml via nebulizer at 6 liters/minute
CO-INTERVENTIONS	0.5 ml of 2.25% Racemic Epinephrine was added to each nebulizer A second dose of the initial treatment could be given at treating MD discretion
OUTCOME	Primary Outcomes: 1. Respiratory Assessment Change Score (RACS): RACS is a sum of the change in the RDAI score plus a standardized score for the change in respiratory rate from 0 to 120 minutes. The change in respiratory rate is assigned 1 point per each 10% change in the respiratory rate. A negative score signifies improvement (See Appendix for score details). 2. Change in oxygen saturation from baseline to 120 minutes. Secondary Outcomes: Rate of admission, rate of return to the ED
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. The patients were randomized into blocks of 4 throughout bronchiolitis season and on a month by month basis. Computer generated randomization
Was randomization concealed?	Yes. Randomization was concealed. The solutions were similar in appearance and smell; stored in identical syringes, labeled only by code number and placed in a research cupboard in the ED. The randomization list was concealed by the pharmacist until the end of the study.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. With the exception that more patients in the hypertonic group were exposed to smoke (HS 34.8% vs NS 13.0%).
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	This was a double blinded study. The physicians and nurses administering the medications were blinded as were the patients. There is no mention whether those analyzing the data were blinded to the study group.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	One of the secondary outcomes included return to the ED and the study discusses that each patient was phoned at 1-week. However, there is no mention of the percentage of patients that were reached for telephone follow-up.
Were patients analyzed in the groups to which they were randomized?	Yes. The study states that the intention to treat principle was used in all analysis.
Was the trial stopped early?	No. The study was not stopped early.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 46 (23 NS, 23 HS)
24 received a second dose (11 NS, 13 HS)
82% RSV positive

PRIMARY OUTCOME
Change in RACS scores (Range 0-17) at 2 hours
Hypertonic Saline: 4.39 (2.62, 6.13)
Normal Saline: 5.13 (3.71, 6.55)
Absolute Risk Difference (NS – HS): 0.74 (-1.45, 2.93)
The authors regarded a change in RACS of > 3 points to be clinically significant.

Change in Oxygen Saturation at 2 hours
Hypertonic Saline: -0.44 (-2.11, 1.23)
Normal Saline: 1.34 (-0.29, 2.99)
Absolute Risk Difference (NS – HS): 1.78 (-0.50, 4.05)

SECONDARY OUTCOMES
Hospital Admission
Hypertonic Saline: 8/23 = 34.7%
Normal Saline: 13/23 = 56.5%
Absolute Risk Difference (NS – HS): 21.7% (-6.6, 45.7%)
Relative Risk (HS/NS): 0.61 (0.32,1.2)

Returns to the ED
Hypertonic Saline: 3/23 = 13.0%
Normal Saline: 4/23 = 17.4%
Absolute Risk Difference (NS – HS): 4.3% (-17.4, 25.8%)
Relative Risk (HS/NS): 0.75. (0.19, 2.98)

Adverse Events: HS only (vomiting 3, diarrhea 1)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence intervals for the primary and secondary outcomes are listed above. The small sample size results in relatively large confidence intervals (lack of precision)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Little information is provided regarding patient demographics. The asthma history, although a high percentage, seems similar to our patient population. However, it is difficult to apply this data to our patients given that the standard of care for bronchiolitis in our patients is supportive care and patients does not routinely include racemic Epinephrine.
Were all patient important outcomes considered?	It seems most relevant to look at hospital admissions, respiratory status, and bounce backs to the ED. However, the study lacks the power to fully evaluate the effect of hypertonic saline on hospital admissions.
Are the likely treatment benefits worth the potential harm and costs?	The study did not show any improvement in patients given hypertonic saline and racemic epinephrine in comparison to those given normal saline and racemic Epinephrine. Adverse events of vomiting and diarrhea occurred in 4/23 (17%) and only in the hypertonic saline group. Adverse events need to be evaluated more closely in a larger population.

CLINICAL BOTTOM LINE

BACKGROUND: Numerous studies have been conducted to evaluate potential therapies for bronchiolitis. These have analyzed the utility of beta agonists, epinephrine and corticosteroids. Unfortunately, these have not proven to be effective. Recent studies of hypertonic saline have suggested that it may decrease length of stay in inpatients. This study was designed to determine the possible effect of one to two doses hypertonic saline (in conjunction with epinephrine) in the emergency department.

CLINICAL QUESTION: In infants with mild to moderate bronchiolitis does 3% Hypertonic saline with Racemic epinephrine when compared to Normal saline and Racemic Epinephrine improve respiratory status and oxygen saturation at 2 hours in the emergency department?

DESIGN/VALIDITY: This study was a well deigned, randomized, double blind controlled trial. Its primary limitation is a small sample size (n =23) in each study group.

PRIMARY RESULTS: The study concludes that in the treatment of mild to moderate bronchiolitis, Hypertonic saline and Epinephrine combined did not improve the RACS score or oxygen saturation when compared to normal saline and epinephrine combined. The study did show decreased hospital admissions with the use of Hypertonic saline (34% HS vs 66% NS) though this was not statistically significant difference

APPLICABILITY: The primary limitation in generalizing this studies results are the small sample size and the inclusion of racemic epinephrine with each dose of normal saline or hypertonic saline. In essence this is a compound intervention and determining the independent effect of the study interventions is difficult.

AUTHOR'S CONCLUSION: "The optimal treatment of bronchiolitis remains unclear. Our study showed no clinically significant improvement in clinical severity with hypertonic saline in the emergency setting compared with normal saline when a maximum of 2 doses were used. However, there seemed to be a trend toward decreased rates of hospitalization in the hypertonic saline group. The ED setting differs from that of the ambulatory or inpatient setting in that inter- actions are constrained by time, space, and resources. The significance of this study is that this venue (the ED) is often the initial point of contact for many infants with bronchiolitis. As this is the first study with hypertonic saline in the emergency setting and the first negative study, the need for further research is clearly evident to determine whether hypertonic saline does, in fact, have a role in the treatment of bronchiolitis in the ED setting."

POTENTIAL IMPACT: It is unlikely that clinical practice will change based on this study given that no clinical significance was found in improving bronchiolitis scores or oxygen saturation with hypertonic saline. The study was not powered to show any significant change in the rate of hospital admissions. The control in this study differs from current practice in our emergency departments for mild to moderate bronchiolitis (supportive care and not routine use of epinephrine). Larger randomized controlled studies in the emergency department should be conducted to address these issues.

APPENDIX: RDAI

RESPIRATORY DISTRESS ASSESSMENT INSTRUMENT (RDAI)							
	POINTS						
	0	1	2	3	4	Score	Max
Wheezing: During Expiration	None	End	1st 1/2	1st 3/4	Throughout		4
Wheezing: During Inspiration	None	Part	Throughout				2
Wheezing: # Lung Fields	0	1 of 2	3 or 4				2
Supraclavicular Retractions	None	Mild	Moderate	Marked			3
Intercostal Retractions	None	Mild	Moderate	Marked			3
Subcostal Retractions	None	Mild	Moderate	Marked			3
					TOTAL SCORE		17
Total Score is the sum of the score for each row. Range 0-17. Higher score = More severe disease							

The Respiratory Assessment Change Score (RACS) is calculated as the sum of the change in the RDAI score and a standardized score for the change in the respiratory rate, with a reduction of 1 unit for a decrease in respiratory rate of 5 to 15%, 2 units for a decrease of 16 to 25%, 3 units for a decrease of 26%-35% and so on. Negative RACS values signify improvement.

BRONCHIOLITIS:
INPATIENT EPINEPHRINE

In infants requiring admission for bronchiolitis does nebulized Epinephrine when compared to Placebo result in a decrease in length of hospital stay or time until ready for discharge?

Efniki Kyvelos, M.D., Michael Mojica, M.D.
January, 2005

Wainwright C, Altamirano L, Cheney M, Cheney J, Barber S, Price D, Moloney S, Kimberley A, Woolfield N, Cadzow S, Fiumara F, Wilson P, Mego S, VandeVelde D, Sanders S, O'Rourke P, Francis P.

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND CONTROLLED TRIAL OF NEBULIZED EPINEPHRINE IN INFANTS WITH ACUTE BRONCHIOLITIS

N Engl J Med. 2003 Jul 3;349(1):27-35.
PubMed ID: 12840089

STUDY DEFINITIONS	
POPULATION	Inclusion: < 12 months (or < 12 months corrected age if premature), clinical diagnosis of bronchiolitis (history of upper respiratory tract infection, clinical findings consistent with bronchiolitis (wheezing, crackles, respiratory distress with chest recession)). Infants with chronic neonatal lung disease associated with prematurity were not excluded. Classified as mild, moderate, or severe by severity score (See Appendix) Exclusion: Cardiac disease, clinically significant respiratory disease (e.g. cystic fibrosis), corticosteroids within 24 hours, bronchodilators within 4 hours, required ventilatory support before consent. Setting: 4 Hospitals (Australia), 4/2000-9/2001
INTERVENTION	3 doses of nebulized single-isomer (4 ml of 1%) Epinephrine at 4-hour intervals within 24 hours after admission
CONTROL	3 doses of nebulized Placebo at 4-hour intervals within 24 hours after admission
CO-INTERVENTIONS	Criteria for Supplemental Oxygen: < 94% oxygen saturation or any combination of clinically significant respiratory distress, a respiratory rate above 60/minute or difficulty feeding. Supplemental Oxygen Terminated: Oxygen saturation consistently > 93% or infant's condition stable for four hours and starting to tolerate oral feeding. Criteria for Intravenous Fluids: Supplemental oxygen required, respiratory rate > 60 per minute, or oral feeding inadequate. Comfort feeding allowed. Intravenous Fluids Terminated: Able to tolerate oral feeding.
OUTCOME	Primary Outcomes: 1. Length of the hospital stay 2. Time until the child was ready for discharge defined as: No supplemental oxygen for 10 hours, minimal or no chest recession, feeding adequately without need for intravenous fluids. Secondary Outcomes: Changes in clinical scores components before and after nebulization therapy Time that supplemental oxygen was required
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized in blocks, stratified for each hospital.
Was randomization concealed?	Yes. Patients received coded samples of identical smell and color. It does not appear that there was an opportunity to bias allocation though the authors did not specifically state that allocation was concealed.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. The experimental and control groups were statistically similar in their baseline health and current medical status (Table 2). Though not statistically significant there were small differences in the severity of illness and the percentage of patients who were RSV positive. Subgroup analysis stratifying for possible differences in these characteristics revealed similar results to the primary analysis.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	There was a potential for those assessing change in the clinical score to identify the Epinephrine group due to the tachycardia it induces. This should not have influenced the primary length of stay outcome.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. This was an inpatient study and patients were followed to discharge.
Were patients analyzed in the groups to which they were randomized?	Yes. An intention to treat analysis included all enrolled patients for which data was available. This included 10 patients who did not receive all 3 Epinephrine doses. In the placebo group 4 patients did not receive the full regimen and 2 patients received other bronchodilators.
Was the trial stopped early?	No. The trial was not stopped early. The sample size determination required 200 infants, with 100 infants in each group and 194 infants were enrolled

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 194, Epinephrine 99, Placebo 95
Mild (54%), Moderate (24%), Severe (22%)

Length of Stay (Overall)
Epinephrine: 58.8 hours, 95% CI (49.4, 70.0 hours)
Placebo: 69.5 hours, 95% CI (59.3, 81.4 hours)
Relative Risk: Epi/Placebo 0.85. 95% CI (0.67, 1.07)

Time until Ready to Discharge (Overall)
Epinephrine: 46.5 hours, 95% CI (38.3-56.5 hours)
Placebo: 47.7 hours, 95% CI (39.0-58.3 hours)
Relative Risk: Epi/Placebo 0.98, 95% CI (0.74, 1.29)

Time to discharge in the subgroup requiring both supplemental oxygen and IV fluids was statistically longer in the Epinephrine group (140 hours) than the Placebo group (80 hours), RR 1.70 (1.1, 2.60).

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The 95% confidence intervals for the primary outcomes are listed above. They indicate there was no statistically significant difference between the study interventions.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Yes. Inclusion/exclusion criteria and patient characteristics appear similar to our population
Were all patient important outcomes considered?	Time until ready to discharge with specific criteria was used to avoid some of the nonclinical influences on hospital length of stay. Subgroup analysis for other therapeutic intervention (oxygen, intravenous fluids) are provided in Table 3. A subgroup analysis corresponding to the severity classification used in Table 2 would have been helpful.
Are the likely treatment benefits worth the potential harm and costs?	There does not appear to be a benefit of Epinephrine. The subgroup of patients who received Epinephrine and required oxygen and intravenous fluids had a significantly increased time to discharge suggesting a possible adverse effect in this group.

CLINICAL BOTTOM LINE

BACKGROUND: Bronchiolitis is the most common lower respiratory tract infection in infants and young children. The lack of effective interventions make it a frustrating disease to manage. The role of bronchodilators is controversial.

CLINICAL QUESTION: In infants requiring admission for bronchiolitis does nebulized Epinephrine when compared to Placebo result in a decrease in length of hospital stay or time until ready for discharge?

DESIGN/VALIDITY: This was a well-designed randomized clinical trial that included 194 patients in the primary intention to treat analysis. 54% of patients were classified as mild, 24% moderate and 22% severe. Patients requiring hospitalization were randomized to receive nebulized Epinephrine or Placebo 3 times within the first 24 hours after admission. Since length of stay can be influenced by many factors, the authors utilized the “time until the child was ready for discharge” (defined as not requiring supplemental oxygen for 10 hours, minimal or no chest recession, feeding adequately, without the need for intravenous fluids as one of the primary outcomes. There were no major validity concerns with the study’s design. A subgroup analysis corresponding to the severity classification used in Table 2 would have been helpful.

PRIMARY RESULTS: Inpatients receiving a regimen of 3 doses of nebulized Epinephrine did not have a significantly different length of hospital stay, time until ready for discharge or improvement in their clinical status. Time until ready to discharge (Epinephrine group: 46.5 hours, 95% CI (38.3-56.5 hours), Placebo group: 47.7 hours, 95% CI (39.0-58.3 hours), Relative Risk (Epi/Placebo) 0.98, 95% CI (0.74, 1.29). Time to discharge in the subgroup requiring both supplemental oxygen and intravenous fluids was statistically longer in the Epinephrine group (140 hours) than the Placebo group (80 hours), Relative Risk 1.70 (1.1, 2.60). No consistent statistically significant change in the respiratory rate or effort score was found from before to after each treatment, although the infants in the Epinephrine group had a slightly lower respiratory-effort score after all three treatments.

APPLICABILITY: A tertiary care hospital and 3 district hospitals enrolled patients and results were similar between the centers. This increases the likelihood that the study’s results are generalizable to many settings for patients meeting the studies inclusion and exclusion criteria.

AUTHOR’S CONCLUSION: “Because there have been no previous large, randomized, controlled trials, the use of bronchodilators for bronchiolitis has been controversial, with multiple small studies reporting different outcomes with different bronchodilators. The evidence from this trial points clearly to a lack of benefit, in either short-term or long-term clinically relevant outcomes, of nebulized epinephrine in infants hospitalized with acute bronchiolitis”

POTENTIAL IMPACT: The study did not reveal either a short term (change in clinical status after treatment) or long term (time until ready for discharge) benefit of repeated doses of Epinephrine for the treatment of inpatient bronchiolitis. Interestingly, Epinephrine prolonged the time to ready for discharge in the subgroup of patients requiring both supplemental oxygen and intravenous fluids. The authors postulate that Epinephrine may increase oxygen utilization and adversely affect the clinical course of disease in this subgroup. While it is tempting to give therapies with a marginal benefit to sicker patients when other therapeutic options do not exist, this study demonstrated that this could be potentially harmful.

APPENDIX

SEVERITY SCORE					
RESPIRATORY-EFFORT SCORE					
	NONE	MILD-MOD	SEVERE	MULTIPLIER	SCORE
Intercostal recession	0	1	2	1	
Subcostal recession	0	1	2	1	
Substernal recession	0	1	2	1	
Tracheal tug	0	1	2	1.5	
Nasal flaring	0	1	2	1.5	
				TOTAL RESPIRATORY EFFORT	
Score 1 (Mild) = 0 - 4.9, Score 2 (Moderate) = 5.0 - 8.9 Score 3 (Severe) = 9-12					
				RESPIRATORY EFFORT SCORE	
OXYGEN SATURATION BREATHING AMBIENT AIR					
Score 0 = 95-100% Score 1 = 90-94% Score 2 = < 90%					
				OXYGEN SATURATION SCORE	
RESPIRATORY RATE COMPARED WITH THAT OF HEALTHY INFANTS OF SAME AGE					
Score 0 = Rates within 2 SD of the mean for age Score 1 = Rates 2-3 SD above or below the mean Score 2 = Rates > 3 SD from the mean					
				RESPIRATORY RATE SCORE	
OVERALL SEVERITY SCORE					
= Respiratory Effort Score + Oxygen Saturation Score + Respiratory Rate Score Mild = Total Score < 2 Moderate = Total Score 2-3 Severe = Total score > 3					

BRONCHIOLITIS:
NEBULIZED EPINEPHRINE AND DEXAMETHASONE

In infants 6 weeks to 12 months of age presenting to the ED with moderate to severe bronchiolitis, does treatment with nebulized Epinephrine and a short course of oral Dexamethasone when compared to placebo or to either medication used alone result in a clinically important decrease in hospital admissions within 1 week?

Carrie Danziger M.D., Adriana Manikian M.D.
August 4, 2009

Plint AC, Johnson DW, Patel H, Wiebe N, Correll R, Brant R, Mitton C, Gouin S, Bhatt M, Joubert G, Black KJ, Turner T, Whitehouse S, Klassen TP; Pediatric Emergency Research Canada (PERC).

EPINEPHRINE AND DEXAMETHASONE IN CHILDREN WITH BRONCHIOLITIS.

N Engl J Med. 2009 May 14;360(20):2079-89.
PubMed ID: 19439742

STUDY DEFINITIONS	
POPULATION	Inclusion: 6 weeks to 12 months, bronchiolitis (first episode of wheezing with signs of an upper respiratory tract infection) and a RDAI (respiratory distress assessment index) score of 4-15. RDAI rates wheezing and respiratory distress on a 0-17 scale (higher scores = more severe illness). Score < 4: very mild illness, Score > 15 very severe illness (See Appendix) Exclusion: Bronchodilator in ED before assessed by a research nurse, received oral or inhaled corticosteroids within 2 weeks, previous episode of wheezing or a diagnosis of asthma, previous bronchodilator use, chronic cardiopulmonary disease, immunodeficiency, severe distress (pulse rate > 200 beats per minute, a respiratory rate > 80 breaths per minute, or an RDAI score > 15), profound lethargy, exposed to varicella within 3 weeks, born at less than 37 weeks with corrected age of < 6 weeks, insurmountable barriers to communication with the family Setting: Children's hospitals (8) part of Pediatric Emergency Research Canada (PERC). Seasonal enrollment: December-April 2004-2007
INTERVENTION	Nebulized Epinephrine and oral Dexamethasone
CONTROL	1. Nebulized Epinephrine and oral Placebo 2. Nebulized Placebo and oral Dexamethasone 3. Nebulized Placebo and oral Placebo Dexamethasone: 1.0 mg/kg in ED then 0.6 mg/kg PO daily x 5 days (max 10 mg) (Provided with the medications, no prescription required) Epinephrine: 3 ml of 1:1,000 with O_2 flow at 8 Liters/min x 2, 20 minutes apart Placebo: Nebulized equivalent volume to Epinephrine PO: Same sweetener as with oral Dexamethasone Co-interventions at treating MD discretion after 90 minutes
OUTCOME	Primary Outcome: Hospital admission up to 7 days after enrollment (including on the day of presentation) Secondary Outcomes: Change in heart, respiratory rate, RDAI score, oxygen saturation from baseline to 30, 60, 120, and 240 minutes Length and severity of symptoms Time to discharge Return to the health care provider for bronchiolitis symptoms within 22 days
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Computer generated to 4 groups in permuted blocks 0f 8-12 and stratified by center.
Was randomization concealed?	Yes. Codes were secured at each center's pharmacy until enrollment and data entry were complete. Packets were visually identical. Drugs and placebo were identical in appearance, volume, weight, odor and taste.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Groups were similar except for 3 factors (Table 1) The Epinephrine plus Dexamethasone group had more patients with personal history and family history of atopy than any other group. The Dexamethasone group had the lowest number (14% vs 9.5%). A sub-analysis revealed that this do not make a difference in the outcome. The Epi plus Dex group (42%) and the placebo group (40.8%) had more smokers in the home than the Epi only (36.2%) and Dex only groups (33.5%). The Dex only group had highest incidence of history of clinically significant disease (7%) while Epi + Dex group had the lowest (3.5%). Extra bronchodilator use was similar among all groups.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The research nurses, physicians and patients were unaware of group allocation. It may have been possible for physicians or nurses to know when patients received epinephrine if they noticed an increase in heart rate.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Telephone follow up using standardized questionnaire until day 22. Only 3 out of 800 patients were lost to follow up.
Were patients analyzed in the groups to which they were randomized?	Yes. Patients were analyzed by Intention to treat: 23 patients in the Epi plus Dex group, and 23 patients in the Dex group were given smaller dexamethasone doses (given 0.8 mg/kg for day 1, and 0.48 mg/kg x 5 days), but were still analyzed with their respective groups. Three patients were excluded from analysis as they were missing primary outcome data (1 from each group At follow-up, the parents of 64/201 (32%) infants had stopped administering the study syrup. For 19/19 of the Epi+Dex group, 20/20 of the Dex group, and 3/12 of the placebo group, the study syrup was stopped so a physician could prescribe oral corticosteroids. These patients were analyzed within their allocated study groups.
Was the trial stopped early	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

HOSPITAL ADMISSION BY DAY 7

	Admission			Admit Rate
	YES	NO		
Epinephrine + Dexamethasone	34	165	199	17.1%
Epinephrine + Placebo	47	152	198	23.7%
Placebo + Dexamethasone	51	148	199	25.6%
Placebo + Placebo	53	148	201	26.4%

Epinephrine + Dexamethasone versus Placebo + Placebo
Risk difference = 26.4 – 17.1 = 9.3%
Relative Risk = 17.1/26.4 = 0.65, 95% CI (0.45, 0.95)

When the results were adjusted for multiple comparisons this was not statistically significant (RR 0.65, 95% CI (0.41 – 1.03)).

The absolute risk difference of 9.3% did not meet the author's criteria of a clinically significant difference of 10%

Neither Epinephrine + Placebo nor Placebo + Dexamethasone reduced the rate of admission compared to Placebo + Placebo

Subgroup-analysis:
There were no statistically significant differences in hospital admission rates in patients with atopy, family history of atopy, RSV status, severity (RDAI > 6), presentation early in illness (< 2 days after onset of symptoms), and pharmacy error (lower Dex dose).

Secondary Outcomes:
RDAI Score: Lower in the Epi+Dex and Epi groups even after adjustment (statistically significant difference)

Respiratory Rate: Significantly lower in the Epi+Dex group only after adjustment

Time to Discharge: Lower in the Epi+Dex group but not after adjustment.

Normal Feeding: Resumed faster in the Epi+Dex and Epi groups. Statistically significant before and after adjustment.

Adverse Events: No significant differences
How precise was the estimate of the treatment effect?
Figure 2: Forest plot. Wide confidence intervals for relative risk, most approaching 1 or crossing 1 – representing no difference between Placebo+Placebo group and the 3 other treatment groups
Admission at day 7, RR = 0.65, 95%CI (0.45, 0.95)
When adjusted for multiple comparison (95%CI (0.41, 1.03), didn't reach statistical significance.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Age and illness severity were similar to our patients, but we can't generalize the results to patients older than 12 months, or those with prior wheezing. Patients were given all study medications. Results for those who need to fill a prescription may differ. The dose of dexamethasone is higher than what we typically use (1 mg/kg vs 0.6 mg/kg) and we typically don't continue dexamethasone for 5 days.
Were all patient important outcomes considered?	Outcomes included hospital admission, RDAI score and vital signs. However, the decision for hospital admission did not follow predetermined criteria and was left at the discretion of the attending physician. Indication for admission such: parental anxiety, poor compliance, severity of respiratory distress, interventions required or length of stay were not provided. Demographic information about the admitted patients (age, day of illness, severity, length of admission) was not provided. The study did not examine the number of admissions within 7 days exclusive of those admitted on the day of presentation.
Are the likely treatment benefits worth the potential harm and costs?	The number needed to treat: 1/ARD = 1/0.093 = 10.75 = 11 (95% CI 6-85). Need to treat 11 infants with nebulized epinephrine and dexamethasone to prevent 1 additional admission compared to placebo. Interpreting a NNT in the absence of a non-statistically significant risk difference is difficult.

CLINICAL BOTTOM LINE

BACKGROUND: The treatment of bronchiolitis with bronchodilators or corticosteroids has not been proven efficacious. This randomized clinical trial attempted to determine if Epinephrine and Dexamethasone in combination improved efficacy compared to placebo or either medication alone.

CLINICAL QUESTION: In infants 6 weeks to 12 months of age presenting to the ED with moderate to severe bronchiolitis, does treatment with nebulized Epinephrine and a short course of oral Dexamethasone when compared to placebo or to either medication used alone result in a clinically important decrease in hospital admissions within 1 week?

DESIGN/RISK OF BIAS: This was a well-designed study that enrolled 800 patients with approximately 200 in each of the 4 study groups in the primary intention to treat analysis. There were some validity concerns. In is unclear from a physiologic standpoint why the combination or these medications would improve efficacy over either medication used independently. Second the primary outcome of admission was poorly defined. It would be important to separate ED and subsequent admissions and better define the indications for admission and interventions required for those discharged and subsequently required admission. Admission was at the discretion of the treating physician. A nonstandard dose of 1 mg/kg Dexamethasone was used in the emergency department.

PRIMARY RESULTS: The study demonstrated a statistically significant absolute risk reduction (Risk Difference = 26.4 – 17.1 = 9.3%) in admissions within seven days only when comparing Epinephrine and Dexamethasone to Placebo. However, when adjusted for multiple comparisons these results were not significant (RR 0.65, 95% CI (0.41 – 1.03). In addition, the absolute risk difference found of 9.3% did not meet the author's predefined clinically significance difference of 10%.

APPLICABILITY: The study is likely applicable to most ED patients who meet study inclusion and exclusion criteria. Patients were given all study medications. Results for those who need to fill a prescription may differ.

AUTHOR'S CONCLUSION: In summary, our multicenter study of 800 infants with bronchiolitis suggests that combined treatment with epinephrine and dexamethasone reduces hospital admissions as well as shortening both the time to discharge and the duration of some symptoms. Given the unexpected synergy we found between epinephrine and dexamethasone and the lack of any apparent benefit when either drug is used alone, our results should be considered exploratory. Although some clinicians consider a trial of a bronchodilator to be standard therapy, published data show, at most, mild transient clinical benefits and no effect on the admission rate. Therefore, confirmation of our findings by a study powered specifically to compare combined epinephrine and dexamethasone therapy with placebo is needed.

POTENTIAL IMPACT: The authors correctly conclude that these results should be considered exploratory and that further studies would be needed before this could be applied to patient care.

APPENDIX: STUDY OUTCOMES

RESPIRATORY DISTRESS ASSESSMENT INSTRUMENT (RDAI)							
	POINTS						
	0	1	2	3	4	Score	Max
Wheezing: During Expiration	None	End	1st 1/2	1st 3/4	Throughout		4
Wheezing: During Inspiration	None	Part	Throughout				2
Wheezing: # Lung Fields	0	1 of 2	3 or 4				2
Supraclavicular Retractions	None	Mild	Moderate	Marked			3
Intercostal Retractions	None	Mild	Moderate	Marked			3
Subcostal Retractions	None	Mild	Moderate	Marked			3
					TOTAL SCORE		17
Total Score is the sum of the score for each row. Range 0-17. Higher score = More severe disease							

The Respiratory Assessment Change Score (RACS) is calculated as the sum of the change in the RDAI score and a standardized score for the change in the respiratory rate, with a reduction of 1 unit for a decrease in respiratory rate of 5 to 15%, 2 units for a decrease of 16 to 25%, 3 units for a decrease of 26%-35% and so on. Negative RACS values signify improvement.

BRONCHIOLITIS:
NON-INVASIVE VENTILATION

In children < 24 months with moderate bronchiolitis who require oxygen, does high-flow warm humidified oxygen (HFWHO) when compared to standard low-flow nasal cannula oxygen, provide enhanced respiratory support as evidenced by a reduction in time to weaning off oxygen and treatment failures?

Katrina Knapp D.O., Laura Papadimitropoulos, M.D.

June 2017

Kepreotes E, Whitehead B, Attia J, Oldmeadow C, Collison A, Searles A, Goddard B, Hilton J, Lee M, Mattes J.

HIGH-FLOW WARM HUMIDIFIED OXYGEN VERSUS STANDARD LOW-FLOW NASAL CANNULA OXYGEN FOR MODERATE BRONCHIOLITIS (HFWHO RCT): AN OPEN, PHASE 4, RANDOMIZED CONTROLLED TRIAL.

Lancet. 2017 Mar 4;389(10072):930-939.,
PubMed ID: 28161016

STUDY DEFINITIONS	
POPULATION	Inclusion: < 24 months presents to emergency department or admitted with moderate bronchiolitis (defined by NWS Health clinical practice guideline). Required supplemental oxygen. 1 of the following: abnormal heart rate, respiratory rate, decreased oxygen saturation or increased work of breathing Included patients with neonatal chronic lung disease on home oxygen but they had to be weaned to their home oxygen baseline. Exclusion: Mild bronchiolitis not requiring oxygen. Severe or life-threatening bronchiolitis. Defined as (any one): witnessed apnea, severe tachypnea (> 70/minute) or bradypnea (< 30/minute), moderate to severe grunting, cyanosis, or pallor. Oxygen saturation < 90% on room air or < 92% on 2L/min oxygen via nasal cannula, tachycardia (> 180/minute) or bradycardia (< 100/minute) Admitted to the ward after ICU management Transferred from other facilities having received supplemental oxygen prior History of asthma, presence of nasal trauma or pneumothorax. Setting: Single Children's Hospital (Australia), 7/2012-5/2015
INTERVENTION	HFWHO (High-Flow, Warm, Humidified Oxygen) delivered through a humidifier and nasal cannula with a flow rate of 1 liter/kg/min (Maximum of 20 Liters/min), 1:1 Oxygen:Air mixture with an approximate FiO_2 of 60%
CONTROL	Cold wall oxygen 100% in the ED (humidified on admission) via infant nasal cannula at low flow to a maximum of 2L/min. Approximate FiO_2 of 30-38%
CO-INTERVENTIONS	Intervention and controls were maintained for at least 3 hours NPO for first hours. Unclear if received intravenous fluids as per protocol
OUTCOME	Primary Outcome: Time to weaning of oxygen (time from randomization to the first sustained room-air observation after oxygen) based on a standardized weaning schedule Secondary Outcomes; Safety: Time from randomization to treatment failure, proportion with treatment failure, serious adverse events, transfer to ICU. Treatment failure was defined as: critically abnormal observations that fell within the red zone on an age appropriate scale for age dependent heart rate or respiratory rate, SpO2 (< 90%), or respiratory distress score quantified as severe while on maximum therapy with clinical decision by treating physician. Escalation procedures were standardized. Parent assessment at 30-day follow up: delayed serious adverse events, subsequent medical care, parental concern with oxygen therapy, and parental rating of child's comfort, ability to feed and sleep. Efficacy: Length of hospital stay, baseline-adjusted heart rate and respiratory rate at 4 hours and 12 hours
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. The patients were randomly allocated (1:1) using a block size of four and stratified for gestational age at birth using three strata: 1. extreme premature (28 weeks or less, 2. premature (from 28 weeks and 1 day to 36 weeks and 6 days) 3. term (37 weeks or more)
Was randomization concealed?	Allocation was concealed in opaque, sealed envelopes. The interventions have visual differences so it was not possible to mask allocation.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Table 1. The baseline characteristics between the two groups appear similar.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study was not blinded since equipment looks different it is impossible to blind anyone involved. The major outcomes would not be influenced by knowledge of the intervention.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Follow up was complete. All patients who were analyzed in the primary and secondary analysis were followed up since the outcomes they were measuring occurred while all patients were in the hospital. The only exception is regarding the 30-day follow up of the parental satisfaction outcomes. There was 89.1% follow up (90/101, ITT analysis) in the HWHO group and 79.2% follow up (80/101, ITT analysis) in the standard therapy group.
Were patients analyzed in the groups to which they were randomized?	Yes. The authors present both an intention to treat and a per protocol analysis (which were similar). For the primary outcome, 101 patients were assigned to HFWHO group and 101 patients were assigned to standard therapy. The per protocol analysis for time to oxygen weaning consisted of 186 children, 92 patients in the HFWHO group and 94 in the standard therapy (16 exclusions).
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 202 (101 in each group)
RSV 57%, Rhinovirus 47%, Adenovirus 10%

Primary Outcome: Time to Oxygen Weaning
Standard Therapy: 24 hours, 95% CI (18, 28 hours)
HFWHO: 20 hours, 95% CI (17, 34 hours)
Risk Difference: 4 hours
The authors considered a 12-hour difference to be clinically significant in their sample size determination
Hazard Ratio: 0.93, 95% CI (0.7, 1.2), p = 0.61

Secondary Outcome:
1. 24-Hour event free survival without treatment failure
Standard therapy: 60%, 95% CI (50, 70%).
HFWHO: 90%, 95%CI (80, 100%)
Risk Difference: 35%
Hazard Ratio: 0.3, 95% CI (0.2, 0.6), p <0.0001

2. Treatment failure (proportion)
Standard therapy: 33% (20 of 33 rescued with HFWHO)
HFWHO: 14%
Risk Difference: 19%, 95% CI (8, 30%)

3. Follow-up
HFWHO: significantly higher comfort and feeding score

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

For the primary outcome, the Hazard Ratio was 0.93 with a 95% CI 0.7-1.2. Since the confidence interval for a Hazard Ratio did includes 1 the difference is not statistically significant. For the secondary outcome of time to treatment failure, the hazard ratio was 0.3 with a 95% CI 0.2-0.6. Since the confidence interval CI for the Hazard Ratio did not include 1 the difference is statistically significant.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. The patients that were enrolled in this study seemed to be similar to our patient population. The inclusion of premature infants and those with chronic lung disease improves generalizability.
Were all patient important outcomes considered?	Yes. All clinically important outcomes were considered.
Are the likely treatment benefits worth the potential harm and costs?	There were no reported serious pressure related adverse advents such as pneumothorax, pressure injuries, bleeding, or deaths. It would be interesting to see if there were any nasal mucosal injuries due to the prongs in the HFWHO group. One would think that the standard therapy group would be less expensive in cost compared to HFWHO. Despite the 16X cost of HFWHO the bed-day costs were equivalent in both arms. This is because there were more failures in the standard therapy group who required rescued with HFWHO or PICU transfer.

CLINICAL BOTTOM LINE

BACKGROUND: There has been an increase in use of High-flow Warm Humidified Oxygen (HFWHO) known in the U.S as High Flow Nasa Cannula Oxygen for bronchiolitis though the evidence to support it use has been primarily from retrospective observational studies. Its efficacy has not been established in randomized clinical trials. In theory, the function of HFWHO is similar to positive end expiratory pressure in that airway pressure would increase the effect alveolar surface area and improve ventilation/perfusion mismatch. The primary use would be to decrease the need for invasive endotracheal intubation but it is not clear if those with moderate disease would benefit.

CLINICAL QUESTION: In children < 24 months with moderate bronchiolitis who require oxygen, does high-flow warm humidified oxygen (HFWHO) when compared to standard low-flow nasal cannula oxygen, provide enhanced respiratory support as evidenced by a reduction in time to weaning off oxygen and treatment failures?

DESIGN/VALIDITY: This was a well-designed pragmatic, open label randomized clinical trial without significant sources of bias that included 202 patients in the primary intention to treat analysis.

HFWHO was delivered through a humidifier and nasal cannula with a maximum flow of 1 liter/kg/min to a limit of 20L/min with a maximum FiO2 of 60%. The standard therapy group was given cold wall 100% oxygen at a flow rate of 2L/min max with an estimated FiO2 of 30-38%. HFWHO is a composite intervention including: warm temperature, humidification, higher flow rates (on therefore pressure) and higher oxygen concentration and the study did not allow for the assessment of the individual or synergistic contributions of each of the components.

The pragmatic study design allowed the inclusion of premature infants as well as those with chronic lung disease requiring home oxygen) as well as premature infants. Moderate bronchiolitis according to the NSW Health practice guideline for bronchiolitis. However, the parameters of the guideline such as work of breathing, tachypnea, grunting could be interpreted differently among providers. Interrater reliability was not assessed.

The primary outcome was time to weaning of oxygen, from randomization to the first sustained room air observation. To eliminate provider variability this outcome was based on standardized weaning criteria. Secondary outcomes included time from randomization to treatment failure, proportion of treatment failures, proportion of serious adverse events, transfer to ICU, length of hospital stay, and adjusted heart rate and respiratory rate for age at 4 and 12 hours. Escalation procedures were also standardized. Though there was no blinding it is unlikely that lack of blinding would influence the mostly objective outcome measures

PRIMARY RESULTS: There was no difference in the primary outcome of time to weaning off oxygen between the HFWHO group (20 hours, 95% CI (17, 34 hours)) and standard therapy group (24 hours, 95% CI (18, 28 hours)). Hazard Ratio 0.93, 95% CI (0.7, 1.2). The authors considered a 12-hour difference to be clinically significant in their sample size determination.

There was a statistically significant difference in the proportion who remained free from treatment failure within 24 hours of admission. HFWHO = 90%, 95%CI (80, 100%), Standard Therapy = 60%, 95% CI (50, 70%). Hazard Ratio 0.3, 95% CI (0.2, 0.6); p<0.0001). In addition, 20 of the 32 patients who deteriorated on standard therapy and then trialed on HFWHO were successfully rescued and did not require transfer to the ICU or more invasive therapy.

Costs were equivalent in both groups despite HFWHO being 16 times the cost of standard therapy. This was because of the higher number of treatment failures in the standard therapy group who then required rescue with HFWHO or ICU transfer. Parents rated significantly higher comfort and feeding score in the HFWHO group.

APPLICABILITY: The patient population that was studied is comparable to the patient population that we treat. It included patients who were premature with chronic lung disease, which is definitely a proportion of the patients who we see with bronchiolitis. The fact that it was a pragmatic study makes it more applicable to routine clinical practice. The definition of oxygen saturation (≤ 94%) requiring supplemental oxygen differs from ours. The American Academy of Pediatrics recommends that practitioners may choose to not use supplemental oxygen for patients with oxygen saturation greater than 90% and that oxygen should be provided in the least invasive method possible to maintain oxygen saturation greater than 90%.

AUTHOR'S CONCLUSION: "In conclusion, this study did not detect a difference in time on oxygen when High-flow warm humidified oxygen (HFWHO) was compared with standard therapy, which suggests that early use of HFWHO does not modify the underlying disease process in moderately severe bronchiolitis. However, HFWHO proved to be safe at the conservative flows and FiO_2 used in this study, and its use prevented intensive care admission in some children for whom standard therapy failed. We caution against the routine use of higher flows or higher FiO_2 in paediatric wards in the absence of trial evidence of safety and effectiveness. This study provides evidence for the use of HFWHO at a maximum of 1 L/kg per min (FiO_2 0.6) in the management of children with bronchiolitis of moderate severity for whom standard therapy with oxygen at 2 L/min has failed or have used HFWHO from the outset."

POTENTIAL IMPACT: The study did not find a statistically difference in the primary outcome of time to weaning of oxygen between the standard therapy group and the HFWHO group indicating that not all patients with moderate bronchiolitis would benefit from HFWHO. However, there was a significant reduction in the proportion with treatment failure within the first 24 hours. In addition, 2/3 of patients who deteriorated on standard therapy were able to be rescued with HFWHO. An important next step would be to identify those patients at higher risk of treatment failure with standard therapy so that they could be targeted for HFWHO therapy.

BRONCHIOLITIS:
ORAL DEXAMETHASONE

In children aged 8 weeks to 23 months with moderate to severe bronchiolitis in the Emergency Department does oral Dexamethasone when compared to placebo result in a decrease in respiratory distress and need for admission at 4 hours?

Katherine Fullerton, M.D., Adriana Manikian, M.D.

September 2008

Schuh S, Coates AL, Binnie R, Allin T, Goia C, Corey M, Dick PT.

EFFICACY OF ORAL DEXAMETHASONE IN OUTPATIENTS WITH ACUTE BRONCHIOLITIS.

J Pediatr. 2002 Jan;140(1):27-32.
PubMed ID: 11815760

STUDY DEFINITIONS	
POPULATION	Inclusion: 8 weeks-23 months, first wheezing episode with respiratory distress and an upper respiratory tract infection, Baseline Respiratory Disease Assessment Instrument (RDAI) rating of ≥ 6 (See Appendix). Exclusion: Previous history of wheezing or bronchodilator therapy, prematurity, neonatal ventilation, chronic lung/cardiac disease, aspiration, neurologic/ neuromuscular problems, immunodeficiency, required immediate airway stabilization, previously oral or inhaled corticosteroids, exposed to varicella within 21 days Setting: Single Pediatric Hospital ED, 11/1997-4/2000 (3, 6month winter periods)
INTERVENTION	Dexamethasone Group: 1 mg/kg oral Dexamethasone syrup (intravenous preparation mixed with cherry flavored syrup) Discharged patients: Oral Dexamethasone 0.6 mg/kg/dose daily for 5 days
CONTROL	Placebo Group: Placebo syrup identical in color, texture, taste and smell to Dexamethasone Discharged patients: Oral Placebo daily for 5 days
CO-INTERVENTIONS	Albuterol: 2.5 mg/dose with oxygen at 6-7 L/min at 0, 30, 60, 120 minutes Vomiting: Dose was repeated x 1 if vomit within 20 minutes, further vomiting resulted in study withdrawal. Admission: Persistent signs of respiratory distress at 240 minutes Received nebulized albuterol only and supportive treatment as indicated. Decisions regarding further treatment and admission made by the blinded ED attending Nasopharyngeal swabs for virology testing
OUTCOME	Outcomes assessed hourly 0-240 minutes in the ED, at patient's home on day 7 and by phone follow up on day 28 Primary Outcome: Respiratory Assessment Change Score (RACS) 0- 240 min Poor response = RACS of ≤ –2 at 240 minutes (See appendix) Secondary Outcomes: Differences in admission rates after 240-minute Changes in oxygen saturation RACS: From Baseline to Day 7
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Randomization was performed in blocks generated via computer.
Was randomization concealed?	Yes. Pharmacists prepared sequential sealed packets for study use. Placebo and dexamethasone were prepared with wild cherry flavor resulting in medications that were identical in color, texture, taste and smell.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. The authors identify that atopy was significantly more common in the Dexamethasone group (83%) than the Placebo group (53%). In the regression analysis, atopy was not an independent predictor of the primary outcome.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Yes. Patient allocation was not revealed until after the study was complete. The placebo and treatment medication were reportedly indistinguishable. Clinicians were not aware of allocation, and were also not aware of the research nurse's assignment of RDAI score. The research nurse was not aware of group allocation.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. All patients were included in the primary analysis at four hours. 3/70 (4.3%) were lost to follow-up at seven days. 5/70 (7.1%) were lost to follow-up at 28 days.
Were patients analyzed in the groups to which they were randomized?	Yes. All 70 enrolled patients were included in the intention to treat analysis. After discharge, 7 infants from the placebo group received corticosteroids from their primary care providers and were included in the analysis of the placebo group.
Was the trial stopped early?	No. The trial was not stopped early.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 70 (Dexamethasone: 36, Placebo: 34)
48/70 (68.6%) discharged from ED

RACS: 0-240 minutes (Intention to Treat Analysis)
Dexamethasone Group: -5.0 ± 3.1
Placebo Group: -3.2 ± 3.7, p = 0.029.
Mean difference: DEX – Placebo = 5.0 – 3.2 = 1.8
Statistically significantly improvement in the DEX group
The authors considered a difference of the mean change score of 2 to be clinically significant

RDAI: 0-240 minutes
Dexamethasone Group: 5.4 ± 2.1
Placebo Group: 7.2 ± 2.8, (p=0.064).
Mean difference: DEX – Placebo = 5.4 – 7.2 = -1.8
Not statistically significant significant

Admission Rate at 4 hours
Dexamethasone Group: 7/36 = 19.4%
Placebo Group: 15/34 = 44.1%, (p=0.039)
Risk Difference: 19.4% - 44.1% = 24.7%, 95% CI (2.9, 43.7%)
Statistically significantly decrease in the DEX group,
No other independent predictors of admission were identified in the regression analysis

There were no statistical differences in outcome measures (RACS, RDAI, hospitalization) at days 7 and 14.

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See the confidence intervals for the mean and risk difference above. The small sample size resulted in wide (imprecise) confidence intervals.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Yes. Ethnic and socioeconomic background were not described. This is an urban hospital with patients similar to ours.
Were all patient important outcomes considered?	For the most part. There was no report of patient tolerability, length of hospital stay or total duration of illness.
Are the likely treatment benefits worth the potential harm and costs?	Perhaps. There were no harmful effects described in this study. Dexamethasone is relatively inexpensive. If respiratory symptoms can be improved leading to improved patient comfort, safety and decreased hospitalization, treatment benefits would be worthwhile. This study showed an improved RCAS and admission rates at four hours. The number needed to treat (NNT = 1/ARD = 1/0.25 = 4) is 4. Need to treat 4 patients with Dexamethasone to avoid one additional 1 hospitalization at 4 hours compared to placebo.

CLINICAL BOTTOM LINE

BACKGROUND: Effective treatments for bronchiolitis are in short supply. Theoretically, corticosteroids could reduce the inflammatory component of the disease. Prior studies on the efficacy of corticosteroids for bronchiolitis have been completed primarily in the inpatient setting, have been small in size or with significant validity concerns.

CLINICAL QUESTION: In children aged 8 weeks to 23 months with moderate to severe bronchiolitis in the Emergency Department does oral Dexamethasone when compared to placebo result in a decrease in respiratory distress and need for admission at 4 hours?

DESIGN/VALIDITY: This was a well-designed study (double-blind, randomized, placebo controlled) in a similar patient population to our own. The study included 70 patients of which 36 were randomized to the Dexamethasone Group and 35 were randomized to the Placebo Group. The study used a higher Dexamethasone dose (1 mg/kg) than used in most prior studies (0.6 mg/kg) though the optimal dose has not been conclusively established. In addition, there was no report of patient tolerability of the study medications, length of hospital stay or total duration of illness.

PRIMARY RESULTS: Patients receiving 1mg/kg PO of dexamethasone in the ED, followed by 0.6 mg/kg/dose PO for 5 days had a statistically significantly decreased rate of hospitalization (Dexamethasone 19.4%, Placebo 44.1%, Absolute Risk Difference: 24.7%, 95% CI (2.9, 43.7%). The number needed to treat (NNT = 1/ARD = 1/0.247 = 4) is 4. Need to treat 4 patients with Dexamethasone to avoid one additional 1 hospitalization at 4 hours when compared to Placebo.

There was also a statistically significant improvement in the Respiratory Assessment Change Score (RACS) at four hours' post-treatment with Dexamethasone (1.8) though this does not meet the authors criteria for a clinically significant difference (2). There were no differences at 7 or 28 days.

APPLICABILITY: The study is like generalizable to ED patients with moderate-severe bronchiolitis who meet the study's inclusion and exclusion criteria.

AUTHOR'S CONCLUSION: "We conclude that children arriving at the emergency department with moderate-to-severe bronchiolitis derive significant clinical benefit and reduced risk of hospitalization from stabilization with dexamethasone 4 hours after administration. Further trials addressing this issue are indicated to confirm this finding."

POTENTIAL IMPACT: It is hopeful to think that a dose of oral dexamethasone in the ED can improve clinical symptoms and results in fewer admissions. This studies results conflict with a Cochrane systemic review published 4 years earlier (2004) that concluded the oral corticosteroids were not beneficial. A subsequent multicenter study in the PECARN network did not identify a benefit of Dexamethasone using the same dose as in this study (See citation below)

SEE ALSO

Corneli HM, Zorc JJ, Mahajan P, Shaw KN, Holubkov R, Reeves SD, Ruddy RM, Malik B, Nelson KA, Bregstein JS, Brown KM, Denenberg MN, Lillis KA, Cimpello LB, Tsung JW, Borgialli DA, Baskin MN, Teshome G, Goldstein MA, Monroe D, Dean JM, Kuppermann N; Bronchiolitis Study Group of the Pediatric Emergency Care Applied Research Network (PECARN).
A Multicenter, Randomized, Controlled Trial of Dexamethasone for Bronchiolitis.
N Engl J Med. 2007 Jul 26;357(4):331-9. PubMed ID: 17652648

APPENDIX: STUDY OUTCOMES

RESPIRATORY DISTRESS ASSESSMENT INSTRUMENT (RDAI)							
	POINTS						
	0	1	2	3	4	Score	Max
Wheezing: During Expiration	None	End	1st 1/2	1st 3/4	Throughout		4
Wheezing: During Inspiration	None	Part	Throughout				2
Wheezing: # Lung Fields	0	1 of 2	3 or 4				2
Supraclavicular Retractions	None	Mild	Moderate	Marked			3
Intercostal Retractions	None	Mild	Moderate	Marked			3
Subcostal Retractions	None	Mild	Moderate	Marked			3
					TOTAL SCORE		17
Total Score is the sum of the score for each row. Range 0-17. Higher score = More severe disease							

The Respiratory Assessment Change Score (RACS) is calculated as the sum of the change in the RDAI score and a standardized score for the change in the respiratory rate, with a reduction of 1 unit for a decrease in respiratory rate of 5 to 15%, 2 units for a decrease of 16 to 25%, 3 units for a decrease of 26%-35% and so on. Negative RACS values signify improvement.

BRONCHIOLITIS:
ORAL DEXAMETHASONE (PECARN)

In infants 2-12 months of age with moderate to severe bronchiolitis, does 1 mg/kg of Dexamethasone when compared to Placebo decrease the need for admission and respiratory distress scores at 4 hours?

Rachel Kowalsky M.D., MPH, Michael Mojica M.D.
August 2007

Corneli HM, Zorc JJ, Mahajan P, Shaw KN, Holubkov R, Reeves SD, Ruddy RM, Malik B, Nelson KA, Bregstein JS, Brown KM, Denenberg MN, Lillis KA, Cimpello LB, Tsung JW, Borgialli DA, Baskin MN, Teshome G, Goldstein MA, Monroe D, Dean JM, Kuppermann N; Bronchiolitis Study Group of the Pediatric Emergency Care Applied Research Network (PECARN).

A MULTICENTER, RANDOMIZED, CONTROLLED TRIAL OF DEXAMETHASONE FOR BRONCHIOLITIS.

N Engl J Med. 2007 Jul 26;357(4):331-9.
PubMed ID: 17652648

STUDY DEFINITIONS	
POPULATION	Inclusion: 2-12 months, first episode of wheezing, no bronchodilator use before the current illness, within 7 days of symptoms onset. Moderate or severe: Respiratory Distress Assessment Instrument (RDAI) ≥ 6 on a scale of 0-17 (See Appendix). Included patients with a history of eczema or a family history of asthma Exclusion: Prior adverse reaction to Dexamethasone, known heart or lung disease, < 36 weeks of gestation, immunosuppression, corticosteroids in prior 14 days, active or recent exposure to varicella, inability of guardian to speak English or Spanish, critically ill infants. Setting: PECARN Network of Children's Hospital EDs (n=20) November-April, 2004-2006 (bronchiolitis season)
INTERVENTION	Single dose of oral Dexamethasone 1 mg/kg (Maximum 12mg)
CONTROL	Identical oral placebo
CO-INTERVENTIONS	Vomiting within 20 minutes recorded, dose not repeated. Additional interventions (e.g. Albuterol or Epinephrine) and testing at treating physician's discretion.
OUTCOME	Primary: Admission at 4 hours after administration of the study medication. (Including those admitted to the ICU prior to 4 hours) Secondary: Change in Respiratory Assessment Change Score (RACS) at 4 hours (see appendix) Tertiary: Change in Respiratory Distress Assessment Instrument (RDAI) at 4 hours. Change in respiratory rate, heart rate, temperature, oxygen saturation at 4 hrs Admitted patients: Length of stay Discharged patients: Unscheduled return visits within 7 days and subsequent hospitalizations (assessed by 7-10 day chart review and phone follow-up). Adverse events
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized by telephone. Infants were allocated to either group using random, permuted blocks stratified by center.
Was randomization concealed?	Yes. Research pharmacists prepared, packaged, and labeled the study drug. The study drug was then allocated by nurses, who did not have access to the randomization codes.
Were patients in the study groups similar with respect to known prognostic factors?	The Dexamethasone group had more RSV positive patients (66.9% vs 57%). It is unclear if this would impact the study results. The Dexamethasone group also had less patients with a family history of asthma or history of eczema in the (63.4% vs 69%). If these patients are more likely to respond to corticosteroids than this could potentially bias the study results in the direction of the Placebo group. However, a subgroup analysis of these factors (Figure 2) did not reveal a statistically significant difference in admission.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Parents, all study clinicians (ED faculty, fellows, and NPs) and research assistants who assessed outcomes were blinded to study group (Figure 1)
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Follow-up data was available for 284/305 (93%) of patients in the Dexamethasone group and 265/295 (89.8%) of patients in the placebo group
Were patients analyzed in the groups to which they were randomized?	An intention-to-treat analysis (600 patients) and a per-protocol analysis (592 patients) were both performed. There was no difference in the results of these 2 analyses. Of note, the per-protocol analysis did not exclude vomiting patients (about 5% of patients). Patients not receiving the intended medication may bias the study results in the direction of the Placebo group.
Was the trial stopped early	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

NEED FOR ADMISSION AT 4 HOURS AFTER TREATMENT

	ADMISSION		
	YES	NO	
DEXAMETHASONE	121	184	305
PLACEBO	121	174	295

Absolute Risk of Admission Dexamethasone group: 121/305 = 39.7%
Absolute Risk of Admission Placebo group: 121/295 = 41%.
Absolute Risk Difference = Dex - Placebo = 39.7% – 41% = -1.3% (-9.2, 6.5), p 0.74
The authors considered a 12% decrease in admission rate to be clinically significant

Figure 2: No difference in admission rate for subgroups: RSV (+) vs (-), Age ≤ 2 vs > 2 years, family history asthma or eczema: (Yes vs No).

2. Change in RACS
Dexamethasone group: -5.3 ± 4.7
Placebo group: -4.8 ± 4.6
Mean Difference: -0.5 (-1.3,0.3), p 0.21.
(The Respiratory Assessment Change Score (RACS) is a function of the Respiratory Distress Assessment Instrument (RDAI) and the percent change in the child's respiratory rate. Negative numbers reflect improvement. A change in RAC score of 2 is generally considered clinically significant) (See Appendix)

3. Change in RDAI Score
Dexamethasone group: -4.4 ± 3.1
Placebo group: -3.9 ± 3.2.
Mean Difference -0.5 (-1.0, -0.1). p 0.03.
(The Respiratory Distress Assessment Instrument (RDAI) Negative numbers reflect improvement: See Appendix)

Other Outcomes
Δ RR: Dexamethasone = Placebo, ARD: -1 (-3.0,1.0), p 0.39
↑ in O2: Placebo > Dexamethasone, ARD: -0.6 (-1.0, -0.1), p 0.02
↓ in HR: Dexamethasone > Placebo, ARD: -8.0 (-12, -5), p < 0.001
↓ in T: Dexamethasone > Placebo, ARD: -0.4 (-0.6, -0.3), p < 0.001
Length of Stay: Dexamethasone: 2.55 days; Placebo: 2.27 days
Subsequent Hospitalization: Dexamethasone: 4.2%; Placebo: 3.8%

Adverse Events
Emesis within 20 minutes: Dex 5.5%, Placebo 4.7%
No GI bleeds, hypertension or complicated varicella.
Pneumonia: Dex = 1, Placebo = 2

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See confidence intervals above. The relatively large sample size resulted in narrow confidence intervals

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. The Inclusion of 20 pediatric hospitals of the PECARN network makes this study results generalizable to other ED's. Applicability to community hospital EDs and outpatient settings is unclear. Non-English speakers were not included. However, there is no biologic basis to believe that their response would differ.
Were all patient important outcomes considered?	Yes. However, one might question the clinical relevance of the RACS and RDAI scores. Inter-rater reliability for score performance and admission were not provided. The study was not powered to control for the subgroups of co-interventions. However, the use of Albuterol and Epinephrine was equally distributed in the two groups. The median day of illness was similar for both groups (Table 2). However, it would have been nice to include a subgroup analysis based on early versus later presenters.
Are the likely treatment benefits worth the potential harm and costs?	This study demonstrated no likely treatment benefits with Dexamethasone. It significantly reduced temperature and heart rate, but the small differences found may not be clinically important. There was also no harm demonstrated in the Dexamethasone group. Adverse effects, primarily vomiting, were equal between the two groups.

CLINICAL BOTTOM LINE

BACKGROUND: Bronchiolitis is the most common cause of infant hospitalization. It is a frustrating disease to manage because so few treatment options exist. A 2002 randomized trial including 70 patients with moderate to severe bronchiolitis demonstrated a 25% (44% versus 19%) reduction in admission at four hours in patients receiving 1 mg/kg of Dexamethasone compared to Placebo. (Shuh, J Pediatrics 2002, PubMed: 11815760). That study is in contrast to a 2004 Cochrane systematic review that concluded the oral corticosteroids were not beneficial (Cochrane Database Syst Rev 2014, PubMed ID: 15266547

CLINICAL QUESTION: In infants 2-12 months of age with moderate to severe bronchiolitis, does 1 mg/kg of Dexamethasone compared to Placebo decrease the need for admission and respiratory distress scores at 4 hours?

DESIGN/VALIDITY: This study was a well-designed, randomized, double-blind, placebo controlled multicenter study in Children's hospitals ED in the PECARN Network. It included 600 patients in the primary intention to treat analysis. The primary validity concern is that it employed subjective outcome measures; the need for admission and change in RDAI and RACS score (see appendix). A 2015 analysis of the validity of the RDAI and RACS scores concluded that the: "RDAI has poor to moderate construct validity, with good discriminative properties but considerable test-retest measurement error. The RDAI and RACS are responsive measures of respiratory distress in bronchiolitis but do not encompass all determinants of disease severity" (Fernandes, Pediatrics 2015, PubMed ID: 25986025). Inclusion of inter-rater reliability would have helped to bolster the validity of these outcomes. In addition, a somewhat higher dose of 1 mg/kg of Dexamethasone was used (though similar to the Shuh study).

PRIMARY RESULTS: 1 mg/kg of Dexamethasone was no different than Placebo in the rate of hospital admission or improvement in respiratory distress score at 4 hours. The absolute risk difference for admission (Dexamethasone – Placebo) was 39.7% – 41% = -1.3% 95% CI (-9.2, 6.5). The authors considered a 12% decrease in admission rate to be clinically significant. There was no statistically significant difference in the change in RACS score at 4 hours (Dexamethasone – Placebo), -5.3 - -4.7. = -0.5, 95% CI (-1.3, 0.3). A change in RACS score of 2 is generally considered clinically significant. The Dexamethasone group demonstrated small improvements in RDAI score, heart rate, oxygen saturation and temperature likely due to the anti-inflammatory effects of corticosteroids. The clinical significance of these small differences is unclear. There was no difference in adverse events, length of stay or subsequent hospitalization.

APPLICABILITY: The Inclusion of 20 Pediatric hospitals EDs in the PECARN network makes this study results generalizable to other academic center ED's. Applicability to community hospital EDs and outpatient settings is unclear.

AUTHOR'S CONCLUSION: "In summary, in our multicenter study of 600 infants from 2 to 12 months of age who had moderate-to-severe bronchiolitis, we found that treatment with 1 mg of oral dexamethasone per kilogram did not significantly alter the rate of hospital admission or the respiratory status after 4 hours of observation. Neither did such treatment affect the length of the hospital stay among infants who were initially admitted, subsequent admissions or unscheduled medical visits, or adverse events. We recommend evaluation of other treatments and preventive strategies for bronchiolitis."

POTENTIAL IMPACT: This study will likely remain the definitive study on the lack of efficacy of corticosteroids for bronchiolitis. A 2013 Cochrane systematic review that included this PECARN study's result in it's meta-analysis concluded that "Current evidence does not support a clinically relevant effect of systemic or inhaled glucocorticoids on admissions or length of hospitalization". (Fernandes, Cochrane 2013, PubMed ID: 23733383)

APPENDIX

RESPIRATORY DISTRESS ASSESSMENT INSTRUMENT (RDAI)							
	POINTS						
	0	1	2	3	4		Max
Wheezing: During Expiration	None	End	1st 1/2	1st 3/4	Throughout		4
Wheezing: During Inspiration	None	Part	Throughout				2
Wheezing: # Lung Fields	0	1 or 2	3 or 4				2
Supraclavicular Retractions	None	Mild	Moderate	Marked			3
Intercostal Retractions	None	Mild	Moderate	Marked			3
Subcostal Retractions	None	Mild	Moderate	Marked			3
					TOTAL SCORE		17
Total Score is the sum of the score for each row. Range 0-17. Higher score = More severe disease							

The Respiratory Assessment Change Score (RACS) is calculated as the sum of the change in the RDAI score and a standardized score for the change in the respiratory rate, with a reduction of 1 unit for a decrease in respiratory rate of 5 to 15%, 2 units for a decrease of 16 to 25%, 3 units for a decrease of 26%-35% and so on. Negative RACS values signify improvement.

BRONCHIOLITIS:
PREDICTING CARE ESCALATION (PERN)

In infants without comorbid conditions with a first episode of clinical bronchiolitis, can demographic, history, physical examination findings and room air oxygen saturation at presentation predict the need for an escalation of care (primarily airway support) in the ED or inpatient setting?

Michael Mojica
January 2019

Freire G, Kuppermann N, Zemek R, Plint AC, Babl FE, Dalziel SR, Freedman SB, Atenafu EG, Stephens D, Steele DW, Fernandes RM, Florin TA, Kharbanda A, Lyttle MD, Johnson DW, Schnadower D, Macias CG, Benito J, Schuh S; Pediatric Emergency Research Networks(PERN).

PREDICTING ESCALATED CARE
IN INFANTS WITH BRONCHIOLITIS.

.

Pediatrics. 2018 Sep;142(3). pii: e20174253.
PubMed ID: 30126934

STUDY DEFINITIONS	
POPULATION	Inclusion: < 12 months, first episode of bronchiolitis (random sample at each site), identified by ICD9 codes for bronchiolitis or RSV bronchiolitis, defined as a viral respiratory infection with respiratory distress Exclusion: Comorbidities: Chronic lung, cardiac, neuromuscular, immune, hepatic or renal Setting: 38 pediatric ED in the International Pediatric Research Network (PERN). US (PECARN, PEM-CRC), Canada (PERC), Australia/New Zealand (PREDICT), England/Ireland (PERUKI), Europe (REPEM)
RULE PARAMETERS	Identified Independent Predictors: Age, poor feeding, apnea, dehydration, nasal flaring and/or grunting, chest retraction, oxygen saturation, respiratory rate
REFERENCE STANDARD	Escalated care in the ED or Inpatient setting. Composite of Admission and: 1. High flow nasal cannula 2. Noninvasive ventilation (CPAP or BPAP) 4. Intubation and ventilation 5. ICU management without airway support (Indications for the interventions were not standardized)
RULE CHARACTERISTICS	Area under the receiver operating characteristic curve Adjusted odds ratio and point score from the logistic regression analysis for the independent predictors of escalated care
DESIGN	Observational: Retrospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. (Table 2). The following predictors were included in the bivariable analysis for an association with escalation of care: age (2 months), sex, prematurity, respiratory distress duration (hours), poor feeding, apnea, dehydration, nasal flaring and/or grunting, chest retractions, respiratory rate (≥ 60), oxygen saturation on room air (< 90%), fever (> 38C)
Were all important predictors present in significant proportion of the study population?	Unclear. (Table 2). Four variables in the bivariable analysis were present in less than 20% of the population. These included: prematurity (13%), apnea (7.9%), dehydration (10.6%) and oxygen saturation < 90% (4.3%). All but prematurity were included as independent predictors in the multivariable regression analysis.
Were the outcome event and predictors clearly defined?	Yes. Standardized definitions of the predictors and outcomes were created for data abstraction.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Unclear. This was a retrospective cohort study. It is very likely that the presence of the predictors was used to indicated the need for escalation of care. Indications for escalation of care were not prespecified.
Was the sample size adequate (including an adequate number of outcome events)?	Yes. The authors targeted 2,000 patients of which 200 had an escalation of care based on 10 independent predictors in the regression analysis and a 10% rate of escalated care. Complete data was available for 2,772 patients of which 261 (9.6%) had an escalation of care.

WHAT ARE THE RESULTS?

N = 2,772 (with complete data for all variables)
N = 261/2,772 (9.6%) with Care escalation (Range: UK/Ireland (3.6%) – Spain/Portugal (15.7%))
Mean age: 4.5 +/- 3.0 months
Mean symptom duration: 2.9 +/- 2.0 days

ESCALATION OF CARE		SITE BREAKDOWN		
MODALITY	#/(%)		# Patients	#ED's
HFNC	164 (5.9%)	PERC	802	8
CPAP or BPAP	47 (1.7%)	PEM-CRC or PECARN	978	10
Mechanical Ventilation	12 (0.7%)	PREDICT	805	8
ICU without airway	38 (1.4%)	PERUKI	841	9
ANY	261 (9.6%)	REPEM	299	3

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS <u>WITH</u> THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SENSITIVITY AND PREDICTIVE VALUE OF A NEGATIVE RULE WITH 95% CONFIDENCE INTERVALS)
HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS <u>WITHOUT</u> THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SPECIFICITY AND PREDICTIVE VALUE OF A POSITIVE RULE WITH 95% CONFIDENCE INTERVALS)

Rule characteristics were not presented

REGRESSION ANALYSIS		
PREDICTOR	ADJUSTED OR (95% CI)	POINT SCORE
Age (2/> 2 years)	2.10 (1.49, 2.97)	1
Poor feeding (Y/N)	1.85 (1.27, 2.71)	1
Oxygen saturation (<90/90%)	8.92 (5.08, 15.66)	5
Apnea (Y/N)	3.01 (1.89, 4.78)	2
Nasal flaring or Grunting (Y/N)	3.76 (2.64, 5.35)	2
Dehydration (Y/N)	2.13 (1.37, 3.30)	1
Retractions (Y/N)	3.02 (1.59, 5.73	2

PROPORTION WITH EACH SCORE REQUIRING ESCALATION (N=2722)					
SCORE	% ESCALATION	% with Score	SCORE	% ESCALATION	% with Score
0	0.5% (1/217)	8.0%	8	40.9% (18/44)	1.6%
1	0.5% (1/199)	7.3%	9	69.7% (23/33)	1.2%
2	2.0% (11/563)	20.7%	10	52.9% (9/17)	0.6%
3	4.5% (33/740)	27.2%	11	81.0% (17/21)	0.8%
4	8.0% (34/423)	15.5%	12	58.3% (7/12)	0.4%
5	16.6% (44/265)	9.7%	13	100% (5/5)	0.2%
6	25.6% (31/121)	4.4%	14	100% (11/11)	0.4%
7	31.4% (16/51)	1.9%			
AUC (Area under the receiver operation curve): 84.7%, 95% CI (81.7%, 86.8%)					

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

Resource utilization in this study could be considered the correct disposition: discharge, admit to inpatient setting, admit to PICU.

RESOURCE UTILIZATION		
SCORE RANGE	% PATIENTS WITH SCORE	ESCALATION RATE
0-1	15%	0.5%
0-2	36%	1.3%
0-3	63%	2.7%
0-4	79%	3.7%
Depending on risk tolerance, one these score ranges could be considered a criteria for discharge and another for admission to the inpatient unit. Higher scores could be considered an indication to be admitted to the ICU.		

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

Bootstrapping validation revealed a corrected AUC of 84.2%, 95% CI (80.3, 88.2%). This was nearly identical the original AUC: 84.7%, 95% CI (81.7%, 86.8%).

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (See Appendix)	☐ I ☐ II ☐ III ■ IV This is a stage IV clinical decision rule. Stage IV rules have been derived only or validated only in split samples, large retrospective databases or by statistical methods. This rule requires further validation before it can be applied clinically.
Does the rule make clinical sense?	Yes. The factors typically associated with bronchiolitis severity are included in the rule. These factors are readily available. Of note, respiratory rate was excluded because of collinearity with retractions.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. This was a retrospective cohort study and there was no assessment of inter-relator reliability of the predictors. Some of the predictors are fairly objective (Age, apnea, oxygen saturation, respiratory rate). However, many of the predictors are open to interpretation (poor feeding, dehydration, nasal flaring and/or grunting, chest retractions) and can vary in severity.
Is the rule applicable to the patients in my practice?	Yes. This multinational, multicenter study included patients from 38 pediatric ED around the world. This likely makes the study's results generalizable to patients in the pediatric ED setting meeting the study's inclusion and exclusion criteria.
Will the rule results change my management strategy?	No. Not at this time. The study requires further validation before it can be used clinically. In addition, it would have been helpful to present the sensitivity and specificity at each score level so that a cutoff could be determined. From an ED standpoint, it would have been helpful to perform a subgroup analysis of those requiring an escalation of care not in the ED.
What are the benefits of applying the rule to my patients?	The score could potentially be used to inform disposition decisions with very low scores for discharge, intermediate scores for admission to the inpatient unit and high score for admission to the PICU.
What are the risks of applying the rule to my patients?	There is always a possibility of making the wrong disposition decision in a patient that subsequently has an escalation of care. This is of particular concern in patients who are discharged.

CLINICAL BOTTOM LINE

BACKGROUND: Bronchiolitis is the most common lower respiratory tract infection and the most common cause of admission in infants. Care is primarily supportive. Approximately 10% will require some airway support including non-invasive ventilation and mechanical ventilation techniques. The ability to identify those at risk for escalation of care would allow for appropriate disposition decisions.

CLINICAL QUESTION: In infants without comorbid conditions with a first episode of clinical bronchiolitis, can demographic, history, physical examination findings and room air oxygen saturation at presentation predict the need for an escalation of care (primarily airway support) in the ED or inpatient setting?

DESIGN/RISK OF BIAS: This was a retrospective cohort study of infants with a first episode of bronchiolitis conducted at 38 pediatrics ED's around the world. Patients with comorbid conditions were excluded. The primary outcome was escalated care in the ED or Inpatient setting. This was a composite outcome of: High flow nasal cannula, CPAP, BPAP, intubation and ventilation or ICU management without airway support. Indications for the interventions were not standardized. These interventions are not of equal importance.

PRIMARY RESULTS: The study included 2,772 patients of which 9.6% (261/2,772) had an escalation in care. The most common airway intervention was HFNC (63%) follow by non-invasive ventilation (CPAP or BPAP)(18%). Seven independent predictors of escalation of care were identified in the regression analysis. These included: age (2 months), poor feeding, oxygen saturation < 90%, apnea, nasal flaring or grunting, dehydration and retractions. Of note, respiratory rate was excluded because it was collinear with retractions. The area under the receiver operation curve was 84.7%, 95% CI (81.7%, 86.8%). The result of the internal validation was similar.

REGRESSION ANALYSIS		
PREDICTOR	ADJUSTED OR (95% CI)	POINT SCORE
Age (2years/> 2 years)	2.10 (1.49, 2.97)	1
Poor feeding (Y/N)	1.85 (1.27, 2.71)	1
Oxygen saturation (<90%/90%)	8.92 (5.08, 15.66)	5
Apnea (Y/N)	3.01 (1.89, 4.78)	2
Nasal flaring or Grunting (Y/N)	3.76 (2.64, 5.35)	2
Dehydration (Y/N)	2.13 (1.37, 3.30)	1
Retractions (Y/N)	3.02 (1.59, 5.73)	2

Sensitivity and specificity at each of the score cutoff points was not provided. 15.3% of patients had a score of 0-1 and an escalation rate of 0.5%. 36% of patients had a score of 0-2 and an escalation rate of 1.3%. These cutoffs could potentially aid in disposition decisions.

PROPORTION WITH EACH SCORE REQUIRING ESCALATION (N=2722)					
SCORE	% ESCALATION	% with Score	SCORE	% ESCALATION	% with Score
0	0.5% (1/217)	8.0%	8	40.9% (18/44)	1.6%
1	0.5% (1/199)	7.3%	9	69.7% (23/33)	1.2%
2	2.0% (11/563)	20.7%	10	52.9% (9/17)	0.6%
3	4.5% (33/740)	27.2%	11	81.0% (17/21)	0.8%
4	8.0% (34/423)	15.5%	12	58.3% (7/12)	0.4%
5	16.6% (44/265)	9.7%	13	100% (5/5)	0.2%
6	25.6% (31/121)	4.4%	14	100% (11/11)	0.4%
7	31.4% (16/51)	1.9%			
AUC (Area under the receiver operation curve): 84.7%, 95% CI (81.7%, 86.8%)					

The study included escalation in the ED as well as an inpatient. The proportion of patients requiring escalation in the ED was only reported for HFNC (30%). From an ED standpoint, it would have been helpful to include a subgroup analysis of patients who had an escalation of care as an inpatient. This would inform the decision to admit the patient to the inpatient floor or ICU.

APPLICABILITY: The multinational, multicenter study included patients from 38 pediatric EDs. This likely makes the study results generalizable to patients in that setting meeting the study's inclusion and exclusion criteria.

This is a stage IV clinical decision rule. Stage IV rules have been derived only or validated only in split samples, large retrospective databases or by statistical methods. This study rule requires further validation before it can be applied clinically.

AUTHOR'S CONCLUSION: "We identified variables measured in the ED predictive of receipt of escalated care for bronchiolitis and derived a clinical risk score with high discriminatory ability and excellent model stability to stratify risk of this outcome during hospital stay. Prospective validation and determination of clinical use are now needed."

POTENTIAL IMPACT: Infants older than 2 months of age with an oxygen saturation greater than 90%, without hydration issues and without retraction, nasal flaring or grunting appear to be at low risk of requiring a subsequent airway intervention. The study requires further validation before it can be used clinically.

APPENDIX: CLINICAL DECISION RULE STAGING

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

BRONCHIOLITIS:
PULSE OXIMETRY ADMISSION CRITERIA

In pediatric patients aged one to twelve months presenting to a tertiary care pediatric ED with bronchiolitis, does an oximetry measurement artificially elevated by 3% when compared to true oximetry values result in lower hospitalization rates?

Sheri-Ann Wynter, M.D., Michael Mojica, M.D.
November 2014

Schuh S, Freedman S, Coates A, Allen U, Parkin PC, Stephens D, Ungar W, DaSilva Z, Willan AR.

EFFECT OF OXIMETRY ON HOSPITALIZATION IN BRONCHIOLITIS

JAMA. 2014 Aug 20;312(7):712-8.
PubMed ID: 25138332

STUDY DEFINITIONS	
POPULATION	Inclusion: Infants 4 weeks to 12 months old with bronchiolitis (first episode of respiratory distress with cough, coryza, wheezing/crackles, and tachypnea or chest retractions), presenting to the ED Exclusion: 1. Children with congenital airway anomalies, neuromuscular, hematologic or cardiopulmonary disease 2. Severe respiratory distress (RDAI score: 8 or 9) 3. Concern for impending respiratory failure 4. Initial oxygen saturation < 88% Setting: Single Pediatric ED (Canada). 3/2008 – 5/2013
INTERVENTION	Altered oxygen saturation value (displayed 3% higher than true value)
CONTROL	True saturation displayed
OUTCOME	Primary Outcome: Hospital admission within 72 hours, which includes: 1. Hospitalization at the index visit or 2. Hospitalization within 72 hours after discharge or 3. Active hospital care in the ED for more than 6 hours. Secondary Outcomes: Supplemental oxygen administration in ED Physician agreement with discharge Length of stay in ED Unscheduled visits for bronchiolitis within 72 hours
DESIGN	Interventional: Randomized clinical trial

ARE THE RESULTS VALID?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized to receive either true oximetry measurements displayed or altered oximetry measurements displayed. Randomization was done via a code using a permuted randomization scheme in blocks of six.
Was randomization concealed?	Yes. Group assignment was emailed by an independent internet service, directing which oximeter to use. The manufacturer altered three of the six oximeters before the study began. Study nurses could not distinguish which oximeter belonged to which study group. Only the director of the respiratory therapy division had the key to which monitors were altered.
Were patients in the study groups similar with respect to known prognostic factors?	Table 1. Demographic and clinical characteristics of the participating infants were mostly similar for the intervention group (altered saturation displayed) when compared to the control group (true oximetry displayed). However, there was a higher percentage of patients with a triage saturation < 94% in the altered oximetry group.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study was double-blinded. Triage nurses did not document the triage saturation in the clinical chart for clinicians to see. Study nurses were blinded to which study group the patient was assigned. The emergency physicians did not know the primary hypothesis of the study. They were told participants had 50% probability of having their oximetry reading altered by a physiologically small amount, but not told in what direction. Parents did see the triage saturation but were not routinely told the meaning of those values.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Study nurses conducted telephone follow-up of all participants who were discharged home at 72 hours after enrollment to identify unscheduled visits for bronchiolitis or delayed hospitalization. Figure on page 714 indicates that there were 0 patients lost to follow-up.
Were patients analyzed in the groups to which they were randomized?	Yes. The primary analysis was performed using the intention-to-treat principle. This was equivalent to a per protocol principle of analysis in this study because once randomized, all patients completed the intervention and none were lost to follow-up.
Was the trial stopped early	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Primary Outcome: Admission within 72 hours of presentation or ED length of stay more than 6 hours

	PRIMARY OUTCOME		
	YES	NO	
ALTERED O_2 SATURATION	26	79	105
TRUE O_2 SATURATION	44	64	108
	70	143	213

Admission Rate: 70/213 = 33%

Absolute Risk (Altered) = 26/105 = 25%
Absolute Risk (True) = 44/108 = 41%
Risk Difference (True-Altered) = 41%- 25% = 16%,
95% CI (3.6-28.4%)

16% fewer patients were admitted in the altered saturation group. The authors considered a difference of 15% to be clinically significant.

Odds (Altered) = 26/79 = 0.329
Odds (True) = 44/64 = 0.687
Odds Ratio (True/Altered) = 0.687/0.329 =2.1, 95% CI(1.2-3.8)

Secondary Outcome (Table 2): Admission subgroup analysis
Only in the ED > 6 hours subgroup was there a statistically and clinically significant difference*

	TRUE	ALTERED	DIFFERENCE (95%CI)	P
Admit Initial	24%	15%	9% (-0.01, 0.2)	0.10
Admit >72 hours	8%	7%	0% (-0.06, 0.08)	0.99
ED > 6 hours	34%	19%	15% (0.04, 0.27)	0.01*

When controlling for age, duration of respiratory distress, triage saturation, and initial RDAI score, there was an Odds Ratio of 4.0, 95% CI, (1.8, 9.6) P=0.00

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Risk Difference (True-Altered) = 41%- 25% = 16% 95% CI (3.6, 28.4%).
This a relatively wide (imprecise) confidence interval
Admission subgroup difference confidence interval are included in table above

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. Study patients were similar in age and disease severity.
Were all clinically important outcomes considered?	Yes. The secondary and exploratory outcomes were comprehensive.
Are the likely treatment benefits worth the potential harm and costs?	NNT = 1/(Absolute Risk Difference) = 1/(0.16) = 6. To benefit one additional patient, you need to alter to the O_2 saturation in 6 patients. Since this is not true intervention a NNT is not applicable to this study.

CLINICAL BOTTOM LINE

BACKGROUND: Bronchiolitis is the leading cause of US hospitalizations for infants. Prior studies have shown that small differences in oxygen saturation may have a large impact on hospitalizations, but have not focused on the emergency department (ED) population.

CLINICAL QUESTION: In pediatric patients aged one to twelve months presenting to a tertiary care pediatric ED with bronchiolitis, does an oximetry measurement artificially elevated by 3% when compared to true oximetry values result in lower hospitalization rates?

DESIGN/VALIDITY: This was a well-designed randomized, double-blinded controlled trial that included 213 patients in the primary analysis. There were no major validity concerns. The primary outcome was an unusual composite outcome (described below). It is also a rare study design using a diagnostic test (oxygen saturation) as an intervention in a controlled trial.

PRIMARY OUTCOME: The primary outcome of the study is hospital admission within 72 hours, which includes:
1. Hospitalization at the index visit,
2. Hospitalization within 72 hours after discharge, and
3. Active hospital care in the ED for more than 6 hours.

16% fewer patients were admitted in the altered (elevated by 3%) saturation group. The authors considered a difference of 15% to be clinically significant. In the subgroup analysis, the results were statistically significant only for active hospital care in the ED for more than 6 hours. The authors did not report additional data to determine if an ED length of stay > 6 hours could be considered equivalent to admission.

APPLICABILITY: The study intervention, an increase in O_2 saturation by 3%, could not be applied clinically. Of note, only 16% of the altered group and 10% of the true group had an initial O_2 saturation < 94% potentially limiting the impact of the study intervention.

AUTHOR'S CONCLUSION: "Among infants presenting to a pediatric emergency department with mild to moderate bronchiolitis, those with an artificially elevated pulse oximetry reading were less likely to be hospitalized within 72 hours or receive active hospital care for more than 6 hours than those with unaltered oximetry readings. This suggests that oxygen saturation should not be the only factor in the decision to admit or discharge and may need to be reevaluated."

POTENTIAL IMPACT: This study in conjunction with a growing body of evidence suggests that oxygen saturation should not be the sole factor in determining Emergency Department disposition decisions.

SEE ALSO:

Principi T, Coates AL, Parkin PC, Stephens D, DaSilva Z, Schuh S.
Effect of Oxygen Desaturations on Subsequent Medical Visits in Infants Discharged from the Emergency Department with Bronchiolitis.
JAMA Pediatr. 2016 Jun 1;170(6):602-8. PubMed ID: 26928704

PNEUMONIA:
C-REACTIVE PROTEIN

In pediatric patients with clinical and radiographically confirmed pneumonia how accurately does C-Reactive Protein distinguish between a bacterial and non-bacterial pneumonia?

Vaishali Shah M.D., Deborah Levine, M.D.
May 2008

Flood RG, Badik J, Aronoff SC.

THE UTILITY OF SERUM C-REACTIVE PROTEIN IN DIFFERENTIATING BACTERIAL FROM NONBACTERIAL PNEUMONIA IN CHILDREN.

Pediatr Infect Dis J. 2008 Feb;27(2):95-9.
PubMed ID: 18174874

STUDY DEFINITIONS	
POPULATION	Study Inclusion: 1. Patient population: 1 month to 18 years 2. CRP quantified for evaluation of a suspected infectious pulmonary process 3. Cutoff serum CRP concentration between 35 and 60 mg/dL 4. Criteria applied to differentiate bacterial from nonbacterial or viral pneumonia 5. Patients acutely ill 6. Chest radiograph obtained as part of initial evaluation. Study Exclusion: 1. Pediatric data could not be extracted or population consisted of adults only 2. CRP was reported as “positive,” as a serum titer, or without identifiable cutoff 3. No language filters were used. Setting: 8 Studies. Published 1989-2002
TEST	CRP > 30 – 60 mg/L.
CRITERION STANDARD	Pneumonia Classification: Pure bacterial, Mixed, or Nonbacterial infections Bacteria pneumonia: Pure bacterial and mixed bacterial and viral infections Non-bacterial pneumonia: Proven viral infections and unknown cause Quality of diagnostic criteria used to differentiate bacterial from non-bacterial pneumonia were scored as follows: Clinical evaluation and 0 Points: Chest XRAY 1 Point: Chest XRAY and Bacterial cultures from any source 2 Points Chest XRAY and Bacterial cultures, viral and/or bacterial immunoassays or nucleic acid assays
OUTCOME	Association of CRP with bacterial pneumonia
DESIGN	Meta-analysis of Prospective Cohort Studies (Diagnostic Testing)

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review include explicitly and appropriate eligibility criteria?	Yes. Study eligibility was based on well-defined inclusion and exclusion criteria. The patient population was children 1 month to 18 years of age who were acutely ill that had a quantifiable CRP checked in the context of a suspected infectious pulmonary process (see study definitions),
Was biased selection and reporting of studies unlikely?	Yes. The authors searched MEDLINE (1996-2006). They also searched the Cochrane database, Embase, CINAHL, LILACS and reviewed reference lists from relevant studies. Search criteria were presented. Two experts in the field reviewed the list of studies found to determine if any major studies were excluded. Publication bias was assessed by the regression test of Egger. Testing demonstrated the absence of publication bias.
Were the primary studies of high methodologic quality?	Yes. The quality of the study was determined across 4 metrics: diagnostic criteria, study design, exclusion of the chronically ill or HIV positive, and the exclusion of patients who recently received antibiotics (Table 1). 8 of 8 were prospective cohort studies 7 of the 8 included trials used a reference criteria of Chest XRAY and bacterial cultures, viral and/or bacterial immunoassays or nucleic acid assays. 3 of 8 studies excluded those with chronic disease or HIV 3 of 8 studies excluded those with recent treatment. Quality was assigned by consensus after the independent review of each study by 2 authors. STARD criteria for reporting the accuracy of diagnostic test studies were not applied though it is unclear if the criteria were available at the time of the meta-analysis.
Were assessment of studies reproducible?	Unclear. The authors first identified 14 studies then selected 8 because many of the studies included the same study population. Of the studies done by the same authors, only one study was included. This was usually the study with the largest number of patients or the study reported in in English. Of the 9 articles excluded, in 7 studies the CRP was not quantifiable and in the other 2 studies the CRP result did not fall within the 30-60 mg/dl range. Although the authors state that the trials were independently reviewed there is no report of an assessment of inter-rater reliability (e.g. kappa statistic) for study inclusion or quality.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

No. Based on the Forest plot in Figure 2 most of the point estimates (odds ratios) were similar with overlapping confidence intervals. One study (Babu, et al 1989) had a higher odds ratio. In a sensitivity analysis (Table 4), the summary odd ratio was lower with this study excluded (1.97, 95% CI (1.07, 3.58)) then the summary odds ratio with the study included (2.58, 95% CI (1.2, 5.55)). The heterogeneity statistics indicated significant heterogeneity of the included study's results (Q 37.7, $p < 0.0001$, $I^2 = 81.4\%$). Given the heterogeneity, the authors utilized the more conservative random effects model.

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 8 Studies, 1,230 patients with pneumonia
41% bacterial (34% bacterial alone, 7% bacterial + viral, 59% viral alone)

<u>Primary Outcome</u>
Odds Ratio(Bacterial/Non-bacterial) for CRP >35-60mg/dl
OR = 2.58; 95% CI (1.20, 5.55)
Children with bacterial pneumonia were 2.58 times more likely to have a CRP > 35-60 mg/dl than children with non-bacterial pneumonia. The confidence interval indicates a statistically significant result.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Yes. CRP is a laboratory test and as such its reproducibility should be satisfactory if the same assay is utilized.
Are the study results applicable to the patients in my practice?	Unclear. The study had a 41% prevalence of bacterial pneumonia. This is approximately twice what is reported by the WHO and CDC. A population with a lower prevalence of bacterial pneumonia would have a significantly lower post CRP probability of bacterial pneumonia than the 64% probability reported in the study. There is also the possibility of spectrum bias. Those with more severe disease could have higher CRP's. A breakdown of pneumonia severity (e.g. by the number of lobes involved) was not provided.
Will the results change my management strategy?	Unclear. CRP is relatively fast and inexpensive test that may be worthwhile in the ED for patients who require intravenous placement of blood obtained. This study's results alone are unlikely to change my decision of when to treat with antibiotics.
Will patients be better off as a result of the test?	The ability to distinguish between a bacterial pneumonia and a non-bacterial pneumonia would help to target antibiotic therapy only where needed and could reduce the rate of antibiotic associated adverse events and potentially reduce the incidence of bacterial resistance.

CLINICAL BOTTOM LINE

BACKGROUND: Distinguishing bacterial from non-bacterial is clinically difficult. Studies addressing this issue often suffer from the lack of a clear criterion standard and the high percentage of patients with co-infection. Traditional we utilize parameters such as age, acuity of onset, season, laboratory, clinical and chest XRAY findings to make management decisions though studies have found these parameters are often of limited diagnostic utility. The ability to distinguish between a bacterial pneumonia and a non-bacterial pneumonia would help to target antibiotic therapy only where needed and could reduce the rate of antibiotic associated adverse events and potential reduce the incidence of bacterial resistance.

CLINICAL QUESTION: In pediatric patients with clinically and radiographically confirmed pneumonia how accurately does C-reactive Protein distinguish between a bacterial and non-bacterial pneumonia?

DESIGN/RISK OF BIAS: This is a somewhat unique study in that it a meta-analysis of diagnostic testing studies and validated methodology for a diagnostic testing meta-analysis and not been established. The study included 8 prospective cohort studies that included 1,230 pediatric patients with pneumonia. Potential biases include the criteria for distinguish between bacterial and non-bacterial pneumonia. Chest XRAY findings and laboratory testing served as surrogate markers for bacterial pneumonia without clearly delineating the findings on chest XRAY. The primary outcome of the study was a summary odds ratio. CRP test results are continuous and it may have been helpful to analyze the overall utility of CRP as an area under the receiver operating characteristic (ROC) curve and then to select a CRP test cutoff based on the desired level of sensitivity and specificity. The authors point out that the data required to do this was not available to them.

PRIMARY RESULTS: Children with bacterial pneumonia were 2.58 times more likely to have a CRP > 35-60 mg/dl than children with non-bacterial pneumonia (Odds Ratio: 2.58; 95% CI (1.20, 5.55).

APPLICABILITY: The study had a 41% prevalence of bacterial pneumonia (possibility of referral) bias). This is approximately twice what is reported by the WHO and CDC. A population with a lower rate of bacterial pneumonia would have a significantly lower post CRP probability of bacterial pneumonia than is reported in the study (64%). In addition, these is a possibility of spectrum bias. Those with more severe disease could have higher CRP's. A breakdown of pneumonia severity (e.g. by the number of lobes involved) was not provided. The study results are also not generalizable to patients who are managed as outpatients as these patients typically do not have blood tests obtained.

AUTHOR'S CONCLUSION: "In summary, this meta-analysis showed that children with serum concentrations exceeding 40 – 60 mg/L were more likely to have bacterial pneumonia than children with lower serum concentrations. Given an a priori probability of 41% for bacterial pneumonia among children presenting with febrile lower respiratory illnesses, a child with clinical and radiographic pneumonia and a high serum CRP has a 64% probability of a bacterial infection."

POTENTIAL IMPACT: Pneumonia is a difficult subject to study because of the lack of a clear and non-invasive criterion standard to distinguish between a bacterial and non-bacterial process. In addition, co-infection is common. CRP is a relatively inexpensive and fast test that can be quickly done in the ED setting in patients who are having blood tests obtained. In the discussion, the authors suggest that "serum CRP concentrations exceeding 40–60 mg/L weakly predict bacterial pneumonia in children".

PNEUMONIA: LEUKOCYTOSIS

In children < 5 years of age with a fever > 102.2 F (≥ 39 C) and a WBC > 20,000 do those in the post-Prevnar7 era, when compared to those in the pre-Prevnar7 era, have lower rates of radiographic pneumonia?

Rachel Kowalsky, M.D., MPH, Jeff Fine, M.D.
January 2009

Rutman MS, Bachur R, Harper MB.

RADIOGRAPHIC PNEUMONIA IN YOUNG, HIGHLY FEBRILE CHILDREN WITH LEUKOCYTOSIS BEFORE AND AFTER UNIVERSAL CONJUGATE PNEUMOCOCCAL VACCINATION.

Pediatr Emerg Care. 2009 Jan;25(1):1-7.
PubMed ID: 19116501

STUDY DEFINITIONS	
POPULATION	Inclusion: < 5 years, temperature ≥ 39 C, CBC obtained with a white blood cell (WBC) count of ≥ 20,000 Not excluded: otitis media, sinusitis, pharyngitis, viral illnesses (mononucleosis, stomatitis, gastroenteritis, bronchiolitis, croup), febrile seizure. Exclusion: Major source of infection (abscess, appendicitis, cellulitis, meningitis, osteomyelitis, urinary tract infection), pneumonia within past 4 weeks, immunodeficiency (sickle cell disease, neoplasia, long-term steroid use, HIV infection, or immunodeficiency syndrome), surgical procedure within 4 weeks, chronic lung disease other than asthma (cystic fibrosis, bronchopulmonary dysplasia, congestive heart failure, chronic aspiration pneumonia). Setting: Single Children's Hospital ED, 1/1996-6/2005
TEST	Fever (102.2 F (≥ 39 C)) and Leukocytosis (WBC > 20,000) Predictors: Age, gender, temperature, oxygen saturation, cough Respiratory rate: tachypnea defined as: ≥ 60 (< 6 months), ≥ 50 (6-12 months), ≥ 40 (1-3 years), ≥ 25 (> 3 years), Lower respiratory tract signs: grunting, flaring, retractions, coarse breath sounds, crackles, rales, rhonchi, wheeze, or decreased aeration/decreased breath sounds
REFERENCE STANDARD	Chest XRAY Pneumonia: Definitive CXR reading of consolidation and/or focal infiltrate(s) Equivocal Pneumonia: Atelectasis, atelectasis versus infiltrate, or reading of equivocal or possible pneumonia. No pneumonia: Peribronchial cuffing, increased interstitial markings, hyperinflation, hilar adenopathy. Occult Pneumonia: Consolidation or infiltrate on CXR in the absence of cough or lower respiratory tract signs.
OUTCOME	Incidence of pneumonia Divided into 2 groups: Pre and Post pneumococcal conjugate vaccine (PCV7) Pre-PCV: 1/1996-12/31/2000 Post-PCV: 1/31/2001-6/30/2005
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Unclear. The study population potentially represents a high risk group (selection bias) in that patients required a fever ≥ 39C, to have a CBC sent and have a WBC > 20,000 and a chest XRAY obtained to be included in the study. There were no predefined criteria for obtained additional testing and it was at the ED providers discretion. In the post Prevnar era the practice of obtaining a screening CBC to identify risk of occult bacteremia declined. Patients who had a CBC obtained in the post Prevnar error could be a particularly high-risk group.
Did investigators compare the test to an appropriate, independent reference standard?	Board-certified pediatric radiologists interpreted all films according to the standards of care, with their interpretation designated as the final clinical reading.
Were those interpreting the test and reference standard blind to the other results?	It is likely that clinicians completed their assessment prior to obtaining an XRAY though it does not explicitly state that they were blinded to the radiology report. It is unclear who much clinical data was available to the radiologist interpreting the XRAY. Foreknowledge of clinical findings has been demonstrated to influence XRAY interpretation
Did all patients receive the same reference standard irrespective of the test results?	Yes. To be included in the study all patients required a chest XRAY.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 1,224 (Pre-PCV7: 889, Post-PCV7: 335)
CBC Obtained: Pre-PCV7: 70%, Post-PCV7: 30%
WBC ≥ 20,000: 13%

Clinical Characteristics:
No statistically significant difference in: Temperature, respiratory rate/tachypnea, oxygen saturation, and WBC in children with and without pneumonia in both the Pre-PCV7 and Post-PCV7 eras.
Note: Vaccination rates increased from 62% in 2002 to 95% in 2005. Results of an analysis comparing 1996-99 to 2002-05 were the same as for the primary analysis.

ALL PNEUMONIA

	PRE-PREVNAR7 1/1996-12/2000	POST-PREVNAR7 1/2001-6/2005
< 5 years (All)	190/889 21% (19, 24%)	61/335 18% (14, 23%)
< 2 years	121/709 17% (14, 20%)	26/254 10% (7, 15%)
2-5 years	69/180 38% (31, 46%)	35/81 43% (32, 55%)

Green = Statistically significant difference, RED = No Statistically Significant Difference

OCCULT PNEUMONIA

	PRE-PREVNAR7 1/1996-12/2000	POST-PREVNAR7 1/2001-6/2005
< 5 years (All)	61/405 15% (12, 19%)	13/147 9% (4, 13%)
< 2 years	38/325 12% (8, 15%)	9/121 7% (3, 14%)
2-5 years	23/80 28% (19, 40%)	4/26 15% (4, 35%)

Green = Statistically significant difference, RED = No Statistically Significant Difference

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	WBC and Temperature are objective findings. Some of the physical exam finding are more subjective. A single pediatric radiologist read the chest XRAY so there was no measure of inter-rater reliability on the study reference standard.
Are the study results applicable to the patients in my practice?	The authors saw more Black and White patients, and less Hispanic patients than at our institution. This may be relevant, as one large study found the risk of pneumonia to be higher in certain ethnic groups at baseline, although there was no evidence of ethnic variation in PCV7 effectiveness.
Will the test results change my management strategy?	Unlikely. As we are no longer screening for occult bacteremia we are no longer obtaining CBC's on well appearing febrile patients. If there is clinical suspicion of pneumonia we would obtain a chest XRAY
Will patients be better off as a result of the test?	Patients with leukocytosis and no lower respiratory tract findings may benefit form a chest XRAY to identify occult pneumonia and provide appropriate antibiotics.

CLINICAL BOTTOM LINE

BACKGROUND: This is a follow-up to a previous study completed by the authors (Bachur, Ann Emerg Med 1999 PubMed ID: 9922412). That study, concluded that children with fever and a leukocytosis (WBC > 20,000) had high rates of lobar infiltrates on chest XRAY. This was true in patients with respiratory distress (40%) and without respiratory distress (20%). This has lead to the utilization of CXR as a screening tool for pneumonia in the febrile patient with leukocytosis. Surveillance data after the implementation of Prevnar 7 revealed a 70% reduction in chest XRAYs with an area of consolidation > 2.5 cm. (Black, Pediatric ID 2000, PubMed ID: 10749457). Because the initial vaccine only covered 7 of the more than 70 pneumococcal serotypes there is a concern for the emergence of non-vaccine serotypes (serotype replacement).

CLINICAL QUESTION: In children < 5 years of age with a fever > 102.2 F and a WBC > 20,000 do those in the post-Prevnar7 era, when compared to those in the pre-Prevnar7 era, have lower rates of radiographic pneumonia?

DESIGN/RISK OF BIAS: This retrospective cohort included 1,224 (pre-PCV7: 889, post-PCV7: 335) patients with fever, leukocytosis and a chest XRAY obtained. This is a highly specific and somewhat arbitrarily defined patient population at high risk of pneumonia. Indications for obtaining laboratory test and chest XRAYS were not standardized and were at the discretion of examining clinicians. Some of the validity concern inherent to a retrospective design need to be considered. For example, vaccination status of the patients was not obtained and was instead state estimates were utilized. In addition, a single radiologist read each XRAY so that reproducibility of the XRAY interpretation could not be assessed.

PRIMARY RESULTS: There was not a statistically significant difference in the clinical characteristics of: temperature, respiratory rate/tachypnea, oxygen saturation, WBC, cough and lower respiratory tract findings in children with and without pneumonia in both the Pre-PCV7 and Post-PCV7 eras. This incidence of occult pneumonia (definitive XRAY reading of pneumonia in the absence of cough or lower respiratory tract signs) was 9% in the post-PCV era. This highlights the limitation of clinical assessment of pneumonia.

In children presenting with high fever and leukocytosis, there was a statistically significant reduction in the rate of radiographic pneumonia in children < 2 years of age (Pre-PCV7: 17% to Post-PCV7: 10%), but there was not a statistically significant difference in those 2-5 years of age (Pre-PCV7: 38% to Post-PCV7: 43%)

APPLICABILITY: This was a very highly selective population and particularly in the post Prevnar era when testing for occult bacteremia decreased significantly in the post-Prevnar era. Clinicians obtained significantly fewer CXR's and CBCs, both of which were entry criteria for the study. It may be that clinicians chose to obtain these studies only on children who were more ill-appearing, which may have biased the study towards a higher rate of pneumonia in the post-Prevnar cohort and making it more difficult to show a protective effect for Prevnar. It may not have been valid to compare these two populations without clear indications for obtaining laboratory testing or chest XRAY. The study's results are not generalizable to all patients with suspected pneumonia.

AUTHOR'S CONCLUSION: "In the era of universal pneumococcal vaccination, pneumonia remains prevalent (18%) in children younger than 5 years with high fever, cough, and/or signs of lower respiratory tract involvement and no other identified source of infection in whom a CBC shows leukocytosis. Occult pneumonia defined as radiographic infiltrate in the absence of cough or lower respiratory tract signs remains a viable diagnosis in young children with high fever and leukocytosis, representing 21% of radiographic pneumonias. Although there has been a significant decrease in the incidence of pneumonia in children younger than 2 years of age with high fever and leukocytosis, 10% of these children had pneumonia in the post-PCV period. On the basis of the results of this study, we conclude that chest radiography should still be considered in highly febrile children younger than 5 years of age with leukocytosis and no other identified treatable source of infection."

POTENTIAL IMPACT: If a CBC is obtained with a WBC > 20,000 in a febrile child it may be prudent to obtain a chest XRAY in both the presence of absence of cough or lower respiratory findings given the limited diagnostic ability of clinical factors to distinguish between those with and without radiographic pneumonia. The generalizability of this study's results to all febrile children or those with a high clinical suspicion of pneumonia less than 5 years is limited. This is particularly true since the introduction of the 2nd pneumococcal vaccine which covers 13 pneumococcal serotypes.

ORIGINAL ARTICLE

Bachur R, Perry H, Harper MB.
Occult Pneumonias: Empiric Chest Radiographs in Febrile Children with Leukocytosis.
Ann Emerg Med. 1999 Feb;33(2):166-73., PubMed ID: 9922412

PNEUMONIA:
POINT OF CARE ULTRASOUND

In pediatric patients (0-21 years) with suspected pneumonia, what are the test characteristics of point of care ultrasound (POCUS) by pediatric emergency medicine physicians with one hour of training for the diagnosis of pneumonia performed when compared to a criterion standard of chest radiograph?

Maria Lame, M.D., Dennis Heon, M.D.
October 2013

Shah VP, Tunik MG, Tsung JW

PROSPECTIVE EVALUATION OF POINT-OF-CARE ULTRASONOGRAPHY FOR THE DIAGNOSIS OF PNEUMONIA IN CHILDREN AND YOUNG ADULTS

JAMA Pediatr. 2013 Feb;167(2):119-25.
PubMed ID: 23229753

STUDY DEFINITIONS	
POPULATION	Inclusion: Birth-21 years, clinical suspicion of pneumonia, chest XRAY obtained Exclusion: Previous diagnosis of pneumonia confirmed by imaging, hemodynamic instability Setting: Single, urban pediatric emergency department, 11/2008-5/2010
INTERVENTION	Point of care lung ultrasound performed by pediatric emergency medicine faculty and fellows with one hour of training (1/2 hour didactic, 1/2 hour hands on training)
CONTROL	Chest XRAY interpretation by pediatric radiologists as consolidation, infiltrate or pneumonia.
OUTCOME	Test characteristics, comparison to clinical findings
DESIGN	Observational: Prospective cohort

ARE THE RESULTS VALID?	
Did participating patients present a diagnostic dilemma?	Yes. Patients in the study were suspected of having pneumonia requiring chest radiography for evaluation though the diagnosis was uncertain.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The investigators compared the test to an independent reference standard, which in this study was a posteroanterior and lateral chest XRAY. Chest XRAY's were interpreted by pediatric radiologists. .
Were those interpreting the test and reference standard blind to the other results?	Study sonologists were blinded to chest radiography results when performing the clinical examination and point-of-care ultrasonography. Radiologists were blinded to clinical examination and ultrasonography results. The study sonologist were not blind to the clinical presentation of the patients and the clinical exam finding did precede the ultrasound.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	All patients underwent a posteroanterior and lateral chest radiography. There was no verification bias.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

	PNEUMONIA		
	CXR POSITIVE	CXR NEGATIVE	
ULTRASOUND POSITIVE[1]	31	18*	49
ULTRASOUND NEGATIVE	5	146	151
	36	164	200
[1]Any positive ultrasound finding			

Prevalence: 36/200 = 18%
Sensitivity: 31/36 = 86%, 95% CI (71-94%)
Specificity: 146/164 = 89%, 95% CI (83-93%)
Likelihood Ratio Positive Test: (31/36/(18/164) = 7.9%, 95% CI (5.0-12.4)
Likelihood Ratio Negative Test: (5/36)/(146/164) = 0.16%, 95% CI (0.07-0.35)
Predictive Value Positive Test: 31/49 = 63%%, 95% CI (49, 75%)
Predictive Value Negative Test: 146/151= 97%%, 95% CI (93, 99%)

*13 of the 18 patients with a positive sonogram and negative XRAY had consolidation of < 1 cm. These may represent false positives or a greater sensitivity of the ultrasound for early pneumonia. The clinical significance of this finding is unclear. If these are excluded from the analysis the specificity increases to 97% (93-99%) and the LR of a positive test increases to 28.2 (11.6-67.6)

Clinical impression had an equivalent sensitivity 84% (69-92) and a lower specificity 39% (32-57). Individual findings such as tachypnea, deceased breath sounds only or crackles only all had sensitivities of < 40%

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	Yes. For ultrasound it is important to determine the consistency of interpretation. A second reviewer that was blinded to clinical information reviewed all of the images. The Kappa statistic was 0.93, 95% CI (0.87-0.99) representing an excellent level of inter-rater agreement. Lung ultrasound represents a technique with a steep learning curve; experience may influence the accuracy of test characteristics. The study included 15 sonologists with different levels of prior ultrasound experience. The sensitivity increased with more experience but this increase was not statistically significant. It would have been helpful to assess inter-rater reliability for chest radiograph interpretation. Variability exists in the interpretation of chest radiographs for the diagnosis of pneumonia.
Are the study results applicable to the patient in my practice?	Yes. The study occurred at an urban pediatric emergency department that is part of a larger academic center. Criteria for who underwent chest CXR was not specified, and was at physician discretion. The patients were recruited by convenience sampling. The prevalence of pneumonia of 18% is consistent with the existing literature. Among 122 examinations performed by those with less ultrasound experience the mean examination time was 8 minutes. Among 78 examinations performed by the more experience sonologist the mean was 7 minutes.
Will the results change my management strategy?	A change in management strategy will depends on your treatment and testing thresholds, Overall, clinical impression showed a sensitivity of 84% and specificity 39%. Other clinical markers had even lower sensitivity and specificity. A negative ultrasound in a patient with low pretest probability could likely be discharged without further imaging or antibiotics.
Will patients be better off as a result of the test?	Potential benefits include less exposure to radiation, real time results and a decrease in ED length of stay. Risks include missing pneumonia. The predictive value of a negative test was 97%. 3% with a negative ultrasound had pneumonia on chest radiograph.

CLINICAL BOTTOM LINE

BACKGROUND: Pneumonia can be missed on physical exam. This may increase the reliance on imaging studies. Growing concerns of potential hazards of radiation have lead for a search for alternate diagnostic tests.

CLINICAL QUESTION: In pediatric patients (0-21 years) with suspected pneumonia, what are the test characteristics of point of care ultrasound (POCUS) by pediatric emergency medicine physicians with one hour of training for the diagnosis of pneumonia performed when compared to a criterion standard of chest radiograph?

DESIGN/RISK OF BIAS: This prospective, observational cohort study enrolled 200 patients with a sufficient clinical suspicion for pneumonia that a chest XRAY was ordered. Test characteristics for point of care ultrasound were reported. In addition, the test characteristics of ultrasound were compared to those of clinical examination findings. Pediatric emergency care physicians with varying levels of experience with ultrasound participated in a 1-hour training session on lung ultrasound and completed a 6-zone lung ultrasonography imaging protocol to determine if pneumonia was present. Ultrasonography finding of pneumonia were defined as lung consolidation with sonographic air bronchograms. Chest XRAY findings of pneumonia were defined as consolidation, infiltrate or pneumonia.

There are no significant validity concerns in the study design. There was an accurate description of the study population. Study sonologists were blinded to chest radiography results when performing the clinical examination and point-of-care ultrasonography. Radiologists were blinded to auscultation and ultrasonography results. However, sonologists were not blinded to physical examination findings. Inter-relater reliability for ultrasound interpretation was excellent (kappa statistic was 0.93 (CI 0.87-0.99).

PRIMARY RESULTS: For patients with lung consolidation on ultrasound exceeding 1 cm, ultrasonography had a Sensitivity of 86%, 95% CI (71%, 94%), Specificity of 97%, 95% CI, (93%, 99%), Positive Likelihood Ratio of 28.2, 95% CI, (11.8, 67.6) and a Negative Likelihood Ratio of 0.1, 95% CI, (0.1, 0.3). It is unclear if an ultrasound finding of consolidation < 1 cm represents a false positive result or clinically important early pneumonias. If these are excluded from the analysis the specificity increases to 97%, 95% CI (93, 99%) and the likelihood ratio of a positive test increases to 28.2, 95% CI (11.6-67.6). Clinical impression had an equivalent sensitivity 84%, 95% CI (69, 92%) but a lower specificity 39%, 95%CI (32, 57%). Individual clinical findings had very poor sensitivity. The mean duration for completion of ultrasound was 11 minutes

APPLICABILITY: Lung ultrasound can be learned quickly (1 hour of training in this study). The Kappa statistic was 0.93, 95% CI (0.87, 0.99) for ultrasound interpretation. Those with more ultrasound experience had a non-statistically significant higher sensitivity. The radiographic pneumonia rate in this study is similar to that found in the emergency department pneumonia literature indicating that the study populations is generalizable to other emergency department populations.

AUTHOR'S CONCLUSIONS: "In summary, clinicians with variable ultrasonography experience can diagnose pneumonia in children and young adults using point-of-care ultrasonography. The specificity of ultrasonographic findings obtained in this manner is high."

POTENTIAL IMPACT: Point of care ultrasound can provide real time diagnosis of pneumonia and potentially decrease ED length of stay. These findings may be particularly relevant in resource scarce settings than lack access to chest radiography.

PNEUMONIA:
LUNG ULTRASOUND META-ANALYSIS (2015)

In children <18 years of age with clinical suspicion for pneumonia (PNA), what is the summarized diagnostic accuracy of Point-of-Care lung ultrasound (LUS) compared to the combination of Chest XRAY and clinical data?

Joshua Beiner, M.D., Deborah Levine, M.D.
May 2015

Pereda MA, Chavez MA, Hooper-Miele CC, Gilman RH, Steinhoff MC, Ellington LE, Gross M, Price C, Tielsch JM, Checkley W.

LUNG ULTRASOUND FOR THE DIAGNOSIS OF PNEUMONIA IN CHILDREN: A META-ANALYSIS.

Pediatrics. 2015 Apr;135(4):714-22.
PubMed ID: 25780071

STUDY DEFINITIONS	
POPULATION	Inclusion: All published, full-text, non-review articles involving children < 18 years of age (including neonatal studies) with clinical suspicion (signs/symptoms) of pneumonia and/or confirmation with CXR/CT with extractable data regarding accuracy of lung ultrasound Exclusion: Studies enrolling ≥ 18years of age, abstracts, unpublished studies, review articles Setting: See individual studies included
INTERVENTION	Pneumonia diagnosis by lung ultrasound
CONTROL	Pneumonia diagnosis by combination of clinical data, lab results or by CXR or CT
OUTCOME	Pooled measurements of diagnostic accuracy
DESIGN	Meta-analysis of 8 prospective cross-sectional studies

ARE THE RESULTS VALID?	
Did the review include explicitly and appropriate eligibility criteria?	Yes, the meta-analysis included all relevant, full-text, non-summary studies in children <18 years of age with a suspicion of PNA after an exhaustive systemic literature search using appropriate search terms. The search strategy was able to return the test studies to assure completeness of the search. Abstracts & unpublished works were excluded as they do not undergo the same peer review process. While neonatal PNA may be a result of different microbiologic organisms, the diagnostic process is similar to PNA in older children, so including 2 neonatal studies seems justified. Though a single study included 9 patients ≥ 18 years of age, the data from these adults were not included in this meta-analysis, warranting its inclusion.
Was biased selection and reporting of studies unlikely?	There was likely some degree of selection bias. On the positive side, the search was not constrained by language or publication date, and queried multiple databases. They included search terms & key words in the supplement allowing for a reproducible search. While excluding unpublished studies and abstracts eliminates data that does not undergo stringent peer revision, it also may allow the opportunity for publication bias. A more likely source of bias was the patient selection, as 5/8 of the studies had a prevalence of PNA(+) ≥ 67%, likely exceeding expected prevalence in all-comers with suspected PNA (15-20%). Two investigators assessed all relevant studies for inclusion criteria. While it was agreed upon a priori that disagreements of inclusion would be settled by a 3rd study member, it did not mention whether there were any such disputes leading to the 8 included studies as depicted in Figure 1.
Were the primary studies of high methodologic quality?	Mostly yes. 2 study investigators independently assessed study quality using the validated 7-item QUADAS-2 criterion. 3 studies were determined to have high risk of bias for the “Patient Selection” domain, including the 2 neonatal studies with “Critically Ill” patients. The Seif El Dien study had high risk of bias across several domains, due to inclusion of “Critically Ill” neonates and because the same radiologist interpreted both the CXR and LUS. This was the only study where the operator and interpreter of LUS were not blinded to CXR findings.
Were assessment of studies reproducible?	Unknown. While discrepancies were resolved with discussion and with consensus using a 3rd investigator, measurement of inter-rater reliability was not included. A kappa statistic on both study inclusion and study quality would have been helpful.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

No. There is significant heterogeneity between studies.

Shah, et al is consistently the study with the most variability, and may account for a considerable portion of the statistical heterogeneity. The authors could have conceivably done a sub-analysis with and without this study to find out the relative weight on summary statistic heterogeneity. While the extremes of the confidence intervals of Sensitivity, Specificity, and Likelihood (-) Forest plots can overlap, this is likely due to the large confidence intervals in certain studies, and does not discount the presence of significant heterogeneity.

The Likelihood (+) and Likelihood (-) pooled measurements both generate Cochrane Q Statistics with $p < 0.10$, indicating statistically significant heterogeneity. The quantitative I^2 for Specificity is in the moderate heterogeneity range while Sensitivity, Likelihood (+), and Likelihood (-) are in the large heterogeneity range. A random effects model should be used when there is significant heterogeneity.

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

The Likelihood (+), Likelihood (-), and respective confidence intervals are very similar. As compared to many point of care ultrasound studies with high specificity and lower sensitivity, Lung ultrasound has high sensitivity & specificity, making it helpful to Rule-In and Rule-Out pneumonia. The size of the consolidation was not reported. Spectrum bias (easier to identify large areas of consolidation) may result in an inflated sensitivity.

TEST CHARACTERISTICS	
Sensitivity	96% , 95% CI (94, 97%)
Specificity	93%, 95% CI (90, 96%)
Likelihood Ratio (+) Test	15.3, 95% CI (6.6, 35.3)
Likelihood Ratio (-) Test	0.06, 95% CI (0.03, 0.11)
The area under the receiver operating characteristic curve: 0.98.	

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. Reproducibility of the point of care ultrasound was assessed in some of the individual studies but is not described for the meta-analysis. Test characteristics were highest with experienced ultrasonographers indicating a learning curve.
Are the study results applicable to the patients in my practice?	Partially. high prevalence of pneumonia While all 8 studies used CXR as part of the reference test, 3/8 used CXR alone, and these studies tended to have lower specificity (84%, 95% CI (80, 88%) These are expected findings due to the well-documented limitation of CXR to detect early and/or small infiltrates. When Chest CT was utilized, it often was in agreement with LUS. The 3/8 studies that used ED patients had a slightly lower sensitivity 94%, 95% CI (88, 98%) and specificity 90%, 95% CI (85,94%). Those 4/8 studies with experienced ultrasonographers performing LUS had the highest sensitivity 97%, 95% CI (93-99%) and specificity 99%, 95% CI (87-95%) while those using trained personnel at all levels had a sensitivity of 95%, 95% CI, (91, 97%) and specificity of 91%, 95% CI (87, 95%). All 8 studies used a similar high-frequency US probe while 3/8 used multiple probes. While 3/8 used non-traditional scanning techniques, at least 6/8 seemingly used techniques equal to or more detailed to the technique used in our ED.Considerations may need to be made in patients with larger habitus as signs of consolidation need to approach the pleura in order to be detected by LUS. Alveolar patterns without large consolidations require clinical correlation as in radiography.
Will the results change my management strategy?	Yes. Considering the lack of an ideal “Gold-Standard” test for diagnosing pneumonia, ultrasound offers an alternative diagnostic tool despite some of the applicability concerns noted above. Some of the imperfect specificity of LUS noted here is likely due to the shortcomings of the CXR as the reference test. Multiple other studies have shown superior test characteristics of lung ultrasound compared to CXR. The most immediate application might be diagnosing pneumonia in patients with low-to-moderate pre-test probability and with positive findings on LUS but negative CXR imaging. Considerations may need to be made in patients with larger habitus as signs of consolidation need to approach the pleura in order to be detected by LUS. Alveolar patterns without large consolidations require clinical correlation as in radiography.
Will patients be better off as a result of the test?	Yes. Benefits include the lack of ionizing radiation and point-of-care availability of the test, making it rapidly available and interpretable. LUS may detect earlier and smaller findings, which may lag on CXR. It may also be able to stratify those eligible for VATS, as LUS can show signs of complicated parapneumonic effusion. Risks include the potential for false positive diagnoses in cases of atelectasis. Like any ultrasound application, it is operator-dependent, though sub-analysis within this meta-analysis demonstrated that limited training leads to proficiency of this particular application.

CLINICAL BOTTOM LINE

BACKGROUND: Pneumonia is a leading cause of illness in children worldwide, resulting in 11-20 million hospitalizations and 1.1 million deaths annually in children < 5 years of age. Despite advances in diagnostic testing and imaging, diagnosis continues to be challenging due to its non-specific presentation and lack of an ideal “gold-standard” test. CXR, though frequently performed for this indication, exposes susceptibly youngsters to ionizing radiation and is not specific enough to rule-out pneumonia when the study is negative. Lung ultrasound may offer a rapid, portable, and inexpensive alternative imaging technique without exposing patients to ionizing radiation.

CLINICAL QUESTION: In children <18 years of age with clinical suspicion for pneumonia (PNA), what is the summarized diagnostic accuracy of point-of-care lung ultrasound (LUS) compared to the combination of CXR and clinical data?

DESIGN/VALIDITY: This was a systematic review and meta-analysis of 8 prospective cross sectional studies including 765 pediatric patients. The 8 studies included in the meta-analysis were generally of high methodologic quality, as supported by the QUADAS-2 assessment, but there were several potential sources of bias. First, they excluded unpublished studies and abstracts. While this eliminates data not subjected to the peer revision process, it also makes publication bias possible. Second, the prevalence of pneumonia in the majority of studies far exceeds that seen in most settings. Third, the various studies used a variety of reference definitions, locations of patient enrollment, and lung ultrasound operators, making the sub-analyses particularly important when assessing applicability of the results. Finally, the qualitative and quantitative evaluations of results heterogeneity were moderate-to-large for each of the pooled measures of accuracy, making this combination of results questionable.

PRIMARY RESULTS: The accuracy of LUS generally approached those of CXR. Sensitivity did not vary significantly regardless of the reference test comparison, setting, or experience of ultrasonographer. Specificity was lowest with: CXR alone as the comparison test, ED setting used for enrollment, and when non-experienced personnel or non-radiologists performed ultrasound. As could be expected, the single study that included all of these variables had the lowest accuracy. In comparison, specificity was highest when: clinical data contributed to reference diagnosis, when hospitalized or critically ill patients were tested, and when experienced ultrasonographers or radiologists performed the study.

TEST CHARACTERISTICS	
Sensitivity	96% , 95% CI (94, 97%)
Specificity	93%, 95% CI (90, 96%)
Likelihood Ratio (+) Test	15.3, 95% CI (6.6, 35.3)
Likelihood Ratio (-) Test	0.06, 95% CI (0.03, 0.11)
The area under the receiver operating characteristic curve: 0.98.	

APPLICABILITY: Likely other ultrasound applications, performance is user dependent and it is not yet clear the amount of training required to develop lung ultrasound proficiency. In addition, it is not yet clear whether ED or radiology departments will take primary responsibility in the ED setting, it is reassuring that multiple studies showed reasonable accuracy after limited training.

AUTHORS CONCLUSIONS: “Despite significant heterogeneity across studies, LUS performed well for the diagnosis of pneumonia in children. Although the sensitivity and specificity are best in the hands of expert users, our study provides evidence of good diagnostic accuracy even in the hands of non-experts. Recommendations to train general pediatricians on LUS for the diagnosis of childhood pneumonia may have an important impact in different clinical settings, especially in resource-poor countries and small primary care clinics where CRs may not be commonly available.”

POTENTIAL IMPACT: Like all POCUS applications, accuracy of LUS is operator-dependent and may be diminished by large patient habitus or alveolar pattern without consolidations. Potential benefits are significant and include ability to detect small effusions and complicated parapneumonic effusions in addition to those noted above. It appears that in patients with moderate-to-high pre-test probability for pneumonia, experienced ultra-sonographers can use LUS to accurately rule-in and rule-out PNA. Further studies should determine whether this can be generalized to patients with a wide range of pre-test probability and when performed by those with more limited ultrasound experience.

PNEUMONIA:
LUNG ULTRASOUND META-ANALYSIS (2018)

In pediatric patients with suspected pneumonia, what is the accuracy of lung ultrasound compared to chest radiography in diagnosing bacterial pediatric community acquired pneumonia?

Shweta Iyer, M.D., Adriana Manikian, M.D.
July 2018

Balk DS, Lee C, Schafer J,Welwarth J, Hardin J, Novack V, Yarza S, Hoffmann B.

LUNG ULTRASOUND COMPARED TO CHEST X-RAY FOR DIAGNOSIS OF PEDIATRIC PNEUMONIA: A META-ANALYSIS.

Pediatric Pulmonology, 2018 Apr 26.
PubMed ID: 29696826

STUDY DEFINITIONS	
POPULATION	Inclusion: Studies that enrolled pediatric patients (< 18 years of age), assessed for bacterial community acquired pneumonia, performed both chest XRAY and lung ultrasound, and had a set reference standard of expert pediatrician clinical diagnosis Exclusion: No original data, abstract only publications, publications with bias, publications not relevant to the study question or not meeting inclusion criteria Setting: A systematic review of relevant literature through August 2017,
INTERVENTION	Lung POCUS (point of care ultrasound) Sonographer: Performed by a variety of users including expert and novice radiologists, pediatric emergency physicians, and expert pulmonologists Probe: Linear alone (5), linear and convex (5), convex only (1), microconvex (1) Technique: Systematic approach to all lung fields. Positioning varied (lateral decubitus or upright). Divided into 6 segments (n=10), 4 segments (n=2)
CONTROL	Reference Standard: “expert pediatrician diagnosis based primarily on a clinical course consistent with bacterial pCAP(pediatric community acquired pneumonia) 8 studies included CXR (chest XRAY) as part of the reference standard 2 studies used chest CT in cases of diagnostic uncertainty
OUTCOME	Test characteristics for lung ultrasound and CXR for the diagnosis of bacterial pCAP
DESIGN	Meta-Analysis: Diagnostic test

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review include explicitly and appropriate eligibility criteria?	Yes. This study had clear definitions for the inclusion and exclusion criteria. However, no specifications of what constituted diagnosis of pCAP are given, except for that the diagnosis was based on clinical course. The intervention criteria within the studies was variable: some studies did not identify whom the sonographers were, simply stating they were ‘experts’, and two studies did not specify sonographer experience at all. Techniques for scanning with ultrasound were variable, as well as LUS findings diagnostic for pCAP.
Was biased selection and reporting of studies unlikely?	Yes. The search included multiple known databases, and the search description was reproducible. The PRISMA study flowchart (figure 1) shows that the selection criteria went through multiple iterations, following QUADAS review, in order to exclude bias and only choose studies meeting inclusion criteria. The study states that possible publication bias was assessed by Funnel plot and Egger's regression intercept but gives no further information about the results of these analyses.
Were the primary studies of high methodologic quality?	No details about the quality of included studies were given. The PRISMA study flowchart (Figure1) indicated that some studies were excluded for “risk of bias.” The information given is that based on QUADAS criteria (to evaluate diagnostic accuracy of studies), all relevant studies were screened for the presence of bias and relevance to the study question by two investigators. A third investigator was invoked to assess any literature for which the initial QUADAS results required consensus.
Were assessment of studies reproducible?	There is no kappa value presented for study inclusion or quality.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

Heterogeneity was assessed by graphic examination of Forest plots and by calculating inconsistency (I^2) and Cochrane's Q. There was wide variability in pCAP incidence from study to study, as evidenced by statistically significant heterogeneity (I^2) for LUS PPV and NPV, and CXR sensitivity and NPV. Therefore, results were not all similar between studies.
The random effects model was used to analyze the raw data for cumulative sensitivity, specificity, NPV, and PPV given the heterogeneity of results. The Freeman-Tukey transformation was used to calculate the weighted summary proportion.
The studies' CI are all similar with overlap, implying that any differences in point estimates are due to chance. The studies' overall CI are narrow, implying precision, except for the CI for NPV.

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 12 studies (1,172 patients)
6 of the 12 studies from Italy, the remaining 6 from around the world.
6 conducted in the ED and 6 on inpatients

Note: The 2x2 tables below were created using the data in Table 2. It is unclear why the test characteristics from these calculations differ from the test characteristics provided in Table 2
Sensitivity = 868/(899) = 96.6%, 95% CI (95.1, 97.6%)

		Pneumonia		
		Yes	No	
Lung Ultrasound	Positive	868	8	876
	Negative	31	265	296
		899	273	1,172

Specificity = 265/(273)) = 97.1%, 95% CI (94.3, 98.5%)
Predictive Value of a Positive Test = 868/(876) = 99.1%, 95% CI (98.2, 99.5%)
Predictive Value of a Negative Test= 265/(296)) = 89.5%, 95% CI (85.5, 92.5%
Likelihood Ratio of a Positive Test = (868/899)/(8/273)= 33.3 (16.6, 65.2)
Likelihood Ratio of a Negative Test = (31/899)/(265/273) = 0.04 (0.03, 0.05)

		Pneumonia		
		Yes	No	
Chest Radiography	Positive	782	3	785
	Negative	117	270	387
		899	273	1,172

Sensitivity = 782/(899)) = 87%, 95% (84.6, 89%)
Specificity = 270/(273)) = 98.9%, 95% CI (96.8, 99.6%)
Predictive Value of a Positive Test = 782/785 = 99.6%, 95% CI (98.9, 99.9%)
Predictive Value of a Negative Test = 270/387 = 69.8%, 95% CI (65, 74.1%)
Likelihood Ratio of a Positive Test = (782/899)/(3/273) = 79.1, 95% CI (25.7, 245)
Likelihood Ratio of a Negative Test = (117/899) = (270/273) = 0.13, 95% CI (0.11, 0.16)

TEST CHARACTERISTICS (PRESENTED IN TABLE 2)		
	LUNG ULTRASOUND	CHEST XRAY
Sensitivity	95.5% (93.6, 97.1%)	86.8% (83.3, 90.0%)
Specificity	95.3% (91.1, 98.3%)	98.2% (95.7, 99.6%)
Predictive Value (+) Test	99.0% (97.9, 99.8%)	99.6% (99.2, 99.9%),
Predictive Value (-) Test	63.1% (40.8, 82.8%)	43.6% (20.6, 68.2%)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the results and their interpretation be satisfactory in my clinical setting?	The meta-analysis included a large sample size, which is beneficial for reproducibility. However, the person performing the ultrasound varied in studies (i.e. expert radiologist, PEM physician, etc.), which is different from our clinical setting, where it would likely always be a PEM physician. There was variability in the LUS findings diagnostic for pCAP as well, beyond visualized consolidations. Additionally, the LUS findings for viral vs. bacterial pneumonia were not clearly defined due to uncertainty over these distinctions. In the studies, the reference standard was expert clinical diagnosis of pneumonia, although no objective criteria were given. The diagnostic criteria may have varied between physicians. Additionally, CXR as a reference standard is suboptimal. Given all these findings, overall these results may not be reproducible in our setting.
Are the study results applicable to the patients in my practice?	The population represented in the study had a high pretest probability having pneumonia, with an 81.6% cumulative incidence of pCAP. Although the individual studies are quite heterogeneous, the overall estimate of pneumonia incidence is quite high in this study. This selected patient population has a high clinical suspicion of PNA; our practice's overall incidence of bacterial pCAP is not very high, and even if we only include children with high clinical suspicion for PNA the numbers may not be similar.
Will the results change my management strategy?	This study had limitations, including variability in: sonographers and level of training, technique, diagnostic lung US findings, and clinical diagnosis of pCAP. In order for lung US to replace CXR, there needs to be standardized training in US for PEM physicians, along with well-established diagnostic US criteria. Additionally, clinical diagnosis of pCAP should follow objective criteria. Due to the above, the current management strategies will likely not change, although many PEM physicians do currently use lung US more frequently for diagnosing or confirming pCAP. This is due to lung ultrasound's ease of use, lack of radiation exposure, and increased sensitivity of pneumonia diagnosis as compared to CXR (which has been shown in prior literature).
Will patients be better off as a result of the test?	Yes. Ultrasound has no radiation exposure involved, unlike chest x-ray. Additionally, physicians can perform the ultrasound as part of their assessment of the patient, theoretically reducing LOS since there is no wait involved for obtaining a CXR and waiting for the interpretation by radiology.

CLINICAL BOTTOM LINE

BACKGROUND: Pediatric community acquired pneumonia (pCAP) is a leading cause of morbidity and mortality in patients, especially under 5 years of age. Although a clinical diagnosis, radiologic confirmation is often obtained with a chest XRAY. Provider-performed lung point of care ultrasound (POCUS has been shown to be accurate in diagnosing pneumonia. Additionally, preliminary studies show that limited US training may be sufficient to become proficient in using lung POCUS for this application.

CLINICAL QUESTION: In pediatric patients with suspected pneumonia, what is the accuracy of lung ultrasound compared to chest radiography in diagnosing bacterial pediatric community acquired

DESIGN/RISK OF BIAS: This was a somewhat poorly designed meta-analysis study with a significant risk of bias. The primary validity concerns are the use of sonographers from different specialties using different ultrasound equipment and techniques and different ultrasound findings for the diagnosis of pneumonia. In addition, the study utilized a poorly defined reference standard of “expert pediatrician diagnosis based primarily on a clinical course consistent with bacterial pediatric community acquired pneumonia”. Some of the studies utilized chest XRAY as part of their reference standard and a few used chest CT in equivocal cases. It is unclear if the outcome assessors were blinded to ultrasound findings. If chest XRAY was part of the reference standard then it is unclear how test characteristics for chest XRAY diagnosis of pneumonia were calculation

The study had explicit and reproducible inclusion criteria. The study included multiple databases as well, and assessed risk of publication bias. The results of the analyses for publication bias were not presented. The studies underwent an assessment for risk of bias using QUADAS but the risk of bias for the included studies was not presented. Inter-rater reliability for study inclusion and quality were not presented. The studies also had a markedly difference prevalence of pneumonia. For these reasons, it is unclear that these studies should be combined from a methodologic standpoint.

PRIMARY RESULTS: As per the article, LUS had a pooled PPV of 99.0% (95%CI: 97.9-99.8) with an I^2 of 63.1%, which was significant. LUS had a pooled NPV of 63.1% (95%CI: 40.8-82.8) with an I^2 of 92.9%, which was significant. CXR had a pooled sensitivity of 86.8% (95%CI: 83.3-90.0) with an I^2 of 66.1%, which was significant. CXR had a pooled NPV of 43.6% (95%CI: 20.6-68.2) with an I^2 of 96.1%, which was significant. The remainder of the results were not significant. The studies’ overall CI are narrow implying precision, except for the CI for NPV.

TEST CHARACTERISTICS (PRESENTED IN TABLE 2)		
	LUNG ULTRASOUND	CHEST XRAY
Sensitivity	95.5% (93.6, 97.1%)	86.8% (83.3, 90.0%)
Specificity	95.3% (91.1, 98.3%)	98.2% (95.7, 99.6%)
Predictive Value (+) Test	99.0% (97.9, 99.8%)	99.6% (99.2, 99.9%),
Predictive Value (-) Test	63.1% (40.8, 82.8%)	43.6% (20.6, 68.2%)

APPLICABILITY: This study had variability in sonographers and level of training, technique, diagnostic lung US findings, and clinical diagnosis of pCAP. Inter-rater reliability for ultrasound interpretation was not presented. Additionally, the selected study population had a high pretest probability of having pneumonia, with an 81.6% cumulative incidence of pCAP. This is far higher than the likely incidence of our ED's population and in the pneumonia literature. The high prevalence also raises the possibility of spectrum bias.

AUTHOR'S CONCLUSION: "This meta-analysis suggests superior sensitivity of lung ultrasound over chest XRAY for the diagnosis of pediatric community acquired pneumonia. Despite a significantly better sensitivity, values for specificity, negative predictive value, and positive predictive value were comparable between lung ultrasound and chest XRAY."

POTENTIAL IMPACT: Due to methodology concerns, it is unclear what information, if any, this study adds to the growing body of evidence on the accuracy of point of care lung ultrasound in the diagnosis of pediatric community acquired pneumonia. POCUS has the potential to be used for diagnostic purposes over CXR given its efficacy, lack of radiation exposure and decrease length of stay due to not having to go somewhere for a chest XRAY and await interpretation.

However, more research is needed for verification, specifically assess pediatric emergency physician POCUS and diagnostic criteria for pneumonia on ultrasound. In particular, lung ultrasound is able to identify sub 1 cm lesions that are not apparent of chest XRAY. The clinical significance of these lesions remains unclear. Standardized training for lung ultrasounds likely needs to be implemented before it can replace chest XRAY as a primary imaging modality. In resource poor settings, where radiology may not be available, point of care ultrasound offers an attractive alternative as some studies have shown it to be more accurate then clinical assessment.

PNEUMONIA:
TACHYPNEA

In children, less than 5 years of age, what is the diagnostic accuracy of tachypnea in predicting radiographic pneumonia?

Carrie Danziger, M.D., George Kristinsson, M.D.
April 2010

Shah S, Bachur R, Kim D, Neuman MI

LACK OF PREDICTIVE VALUE OF TACHYPNEA IN THE DIAGNOSIS OF PNEUMONIA IN CHILDREN.

Pediatr Infect Dis J. 2010 May;29(5):406-9.
PubMed ID: 20032805

STUDY DEFINITIONS	
POPULATION	Inclusion: ≤5 years, CXR obtained for suspicion of pneumonia Exclusion: CXR obtained for indications other than pneumonia: Cardiac disease, trauma, pneumothorax, foreign body aspiration Patients at increased risk for pneumonia: Sickle cell disease, cardiac disease, immunodeficiency, cystic fibrosis, chronic lung disease other than asthma, or severe neurologic disorder. Setting: Single Children's Hospital ED, 11/2006-8/2008
TEST	Tachypnea: 1. Mean triage respiratory rate by age group 2. Age-defined tachypnea by World Health Organization (WHO): RR ≥ 60 if < 2 months, RR > 50 if 2 -12 months, RR ≥ 40 if 1 to 5 years 3. Physician assessed tachypnea
REFERENCE STANDARD	Chest XRAY interpretation by board certified pediatric radiologist. No Pneumonia: Normal chest, normal radiograph, clear lungs, no acute pulmonary findings, atelectasis or peribronchial cuffing. Pneumonia: Consolidation, infiltrate, pneumonia, and atelectasis versus infiltrate, atelectasis versus pneumonia.
OUTCOME	Test Characteristics: Stratified by age: 2 months, 2-12 months, 1-5 years. Rate of pneumonia with and without tachypnea by WHO age categories
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. A XRAY was obtained because clinical evaluation resulted in a suspicion for pneumonia It is not known if physical exam findings strongly supported the diagnosis of pneumonia or why the XRAY was ordered.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The reference standard was a chest XRAY interpreted by a board certified Pediatric Radiologist. A Final reading was obtained from the electronic medical record. Equivocal radiographs (e.g. atelectasis vs pneumonia) were included to minimize misclassification of radiographic pneumonia as a negative study. There was no Kappa statistics presented to assess the reproducibility of the radiologist interpretation.
Were those interpreting the test and reference standard blind to the other results?	The study questionnaire was filled out by the examining physician prior to obtaining the radiograph. Triage nurses also documented the RR before radiograph. It was not stated whether the radiologists were aware of clinical characteristics of the patients. XRAY interpretation has been shown to vary with the amount of clinical information available to the radiologist.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	Yes. All patients had a chest x-ray

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 1,622
235 (14.5%) with radiographic pneumonia
Age: < 2 months (6%), 2-12 months (32%),1-5 years (62%)
Symptoms: Cough (87%), fever (71%)
Admission: 24%

Triage Respiratory Rate:
All: No difference in those with and without pneumonia
1-5 years: Pneumonia > NO Pneumonia (statistically significant though mean difference was only 3.1 breaths/minute)

WHO TACHYPNEA CRITERIA: ALL AGES

	PNEUMONIA		
	YES	NO	
TACHYPNEA: YES	92	359	451
TACHYPNEA: NO	140	1,018	1,158
	232	1,377	1,609

Prevalence: 232/1,377 = 16%
Sensitivity: 92/232 = 40%, 95% CI (33, 46%)
Specificity: 1018/1377 = 74%, 95% (CI 83, 98%)
Predictive Value (+) Test: 92/451= 20%, 95%CI (17, 24%)
Predictive Value (-) Test: 1018/1158 = 88%, 95% CI (86, 90%)
Likelihood Ratio (+) Test: (92/232)/(359/1,377) = 1.5, 95% CI (1.27, 1.82)
Likelihood Ratio (-) Test: (140/232)/(1,018/1,377) = 0.8, 95% CI (0.73, 0.91)

Physician Respiratory Rate:
All age categories: No difference in those with and without pneumonia

Patients without Wheezing:
Nurse Triage: No difference
WHO categories: Statistically significant difference in pneumonia in those with tachypnea (33.1%) and those without tachypnea (19.5%).
Risk Difference: 13.7% 95% CI (6.4, 21.6%)
SN: 33%, SP 81%, PV(+) 17%, PV(-) 86%, LR(+) 1.7, LR(-) 0.83

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Unclear. Children's respiratory rates can vary significant based on factors not related to underlying pulmonary disease. The reproducibility of the respiratory rates used in the study was not assessed.
Are the study results applicable to the patients in my practice?	Yes. Patients were from an urban Pediatric Emergency Department similar to ours. However, indications for ordering an XRAY are unknown.
Will the test results change my management strategy?	Unlikely. Respiratory rate will continue to be used in conjunction with other clinical signs (e.g. fever, retractions, crackles, hypoxia, decreased breath sounds) to decide whether to obtain a chest radiograph.
Will patients be better off as a result of the test?	Tachypnea is not sufficiently sensitive or specific to be the sole indication to obtain a chest XRAY

CLINICAL BOTTOM LINE

BACKGROUND: The World Health Organization has developed guidelines to help identify children with pneumonia in developing nations chest radiographs may not be available. Children with cough or difficulty breathing are assessed for risk of pneumonia based on the child's age and respiratory rate. Prior studies demonstrate that these guidelines help to detect 80% of children in the developing world who require antibiotics for pneumonia.

CLINICAL QUESTION: In children, less than 5 years of age, what is the diagnostic accuracy for tachypnea in predicting radiographic pneumonia?

DESIGN/RISK OF BIAS: This prospective observational study aimed to determine at the accuracy of tachypnea as a sole predictor of radiographic pneumonia. It included 1,622 patients of which 235 (14.5%) had a radiographic pneumonia. They defined tachypnea as: the mean triage respiratory rate, physician-assessed respiratory rate, and age-specific World Health Organization criteria for tachypnea based on age category. Radiographs were interpreted by a board certified Pediatric Radiologist. There were no pre-defined indications for radiography though the rate of pneumonia (14.5) is consistent to rates found in the pneumonia literature.

PRIMARY RESULTS: There was no statistically significant difference in the mean triage respiratory rate in patients with and without pneumonia. The World Health Organization tachypnea by age category was poorly sensitive (Sensitivity: 40%, 95% CI (33, 46%) and non-specific (Specificity: 74%, 95% CI (83, 98%). Essentially tachypnea risk stratified a group with 16% prevalence of pneumonia into a high risk group (20% risk of pneumonia, Predictive Value (+): 20%) and a low risk group (12% risk of pneumonia, 1- Predictive Value (-): 1–0.88 = 12%). In the 1-5-year-old age group there was a statistically significant higher rate of pneumonia in those with tachypnea (43.6%) and those without tachypnea (28.4%). Absolute risk difference: 43.6-28.4 = 15.2%, 95% CI (7.6, 23.1%). However, the sensitivity and specificity were roughly equivalent to that see for all age categories combined. The test performance of tachypnea did not improve when those with wheezing were excluded.

APPLICABILITY: The study results are likely generalizable to patients meeting the study's inclusion and exclusion criteria. The study would have benefited from an assessment of the reproducibility of both respiratory rate and XRAY interpretation.

AUTHOR'S CONCLUSION: "Tachypnea is not a sensitive indicator of pneumonia in a modern, readily accessible health care system. However, children with tachypnea as defined by the age-specific cut-points set forth by the WHO are more likely to have radiographic pneumonia than children without tachypnea. The subjective assessment of tachypnea may be useful in the evaluation of pneumonia risk among children without wheeze."

POTENTIAL IMPACT: Respiratory rate with or without wheezing should not be the sole factor determining the need for a Chest XRAY. We should continue to use tachypnea in conjunction with other clinical signs (i.e. retractions, crackles, hypoxia, decreased breath sounds) to determine the need for chest radiography in children less than 5 years.

PULMONARY EMBOLISM:
PERC CRITERIA VALIDATION (ADULTS)

In adult patients with a low probability of suspected pulmonary embolism what are the rule characteristics of the Pulmonary Embolism Rule-Out Criteria (PERC Low Risk Criteria) in identifying patients with and without pulmonary embolism?

Joanne Agnant M.D., Kari Posner, M.D.
August 7, 2012

Singh B, Parsaik AK, Agarwal D, Surana A, Mascarenhas SS, Chandra S.

DIAGNOSTIC ACCURACY OF PULMONARY EMBOLISM RULE-OUT CRITERIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Ann Emerg Med. 2012 Jun;59(6):517-20.e1-4.
PubMed ID: 22177109

STUDY DEFINITIONS	
POPULATION	Inclusion: Studies that reported diagnostic performance of PERC to rule out pulmonary embolism, original research, conducted in the ED. Data extracted: study characteristics (author, country, publication year, number of patients, study settings, study design, description of study participants, and duration of follow-up), subject selection (inclusion and exclusion criteria), PERC classification, outcome definition and measurement, outcomes in PERC positives and negatives and follow-up. Exclusion: None specified Setting: 11 studies from 6 countries (United States, United Kingdom, Switzerland, France, Belgium, New Zealand)
RULE PARAMETERS	PERC RULE CRITERIA Age < 50 years Pulse < 100 beat/minute $Sp0_2$ > 94% No unilateral leg swelling No hemoptysis No surgery or trauma within 4 weeks No previous DVT or PE No oral hormone (OCP) use
REFERENCE STANDARD	The studies used a wide variety of criterion standards for the confirmation of pulmonary embolism. This included: CT angiography, extremity ultrasound for venous thromboembolism, V/Q scans, pulmonary angiogram and autopsy.
OUTCOME	Primary Outcome: PERC Rule characteristics
DESIGN	Systematic review and meta-analysis of clinical decision rules

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review include explicitly and appropriate eligibility criteria?	Yes. The investigators state that, without language restrictions, they selected studies that reported diagnostic performance of PERC to rule out pulmonary embolism (PE). The only included original research conducted in the emergency department setting.
Was biased selection and reporting of studies unlikely?	Yes. The authors searched EMBASE, MEDLINE, SCOPUS, Web of knowledge, and all of the EBM reviews, including Cochrane from ~1948 to 2011. They also hand-searched references cited in potentially eligible articles and the previous 2 years' conference proceedings of major EM organizations. They also performed Pubmed searches of authors of identified abstracts to locate full articles otherwise missed. They did not mention speaking to any experts in the field for unpublished studies. The authors report as a limitation that they could not assess the possibility of publication bias since there were fewer than 20 studies included in this review.
Were the primary studies of high methodologic quality?	Yes. See Table E2 in the supplementary materials. The QUADAS criteria do not result in a summary score. Most of the QUADAS criteria was answered yes for almost all of the studies. The one exception was the criteria for "Was there an explicit interpretation of PERC by clinicians in practice without knowledge of the outcome?". This was answered no for all of the studies.
Were assessment of studies reproducible?	Two investigators independently screened the titles and abstracts of eligible articles and then the full articles. Inter-observer agreement for study inclusion was excellent with a Kappa of 0.94 (abstracts) and 0.80 (full texts). Two investigators graded the methodology quality of the studies, using the QUADAS criteria. The investigator agreement on methodological quality of the articles was good with a kappa of 0.66.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

The sensitivities, specificities, the likelihood ratios of a positive test, and the likelihood ratios of a negative tests are displayed on Forrest plots in Figure 2. This figure indicates significant heterogeneity in specificity and the likelihood ratio of a positive test. The I^2 statistics for specificity and likelihood ratio of a positive test are 97.3% and 84.6% indicating significant heterogeneity. (An I^2 statistic > 50% represents substantial heterogeneity). A more conservative random-effects model was used to calculate pooled likelihood ratios.

How well did the rule correctly identify patients <u>with</u> the primary outcome? How well did the rule correctly identify patients <u>without</u> the primary outcome? How precise was this measurement?

N = 11 studies, 13,885 patients
10% prevalence of PE.
56% women
Mean age of 52.9 years
Follow-up from 14 to 90 days.

	PULMONARY EMBOLISM		
	YES	NO	
PERC RULE (+)	1,349	9,620	10,969
PERC RULE (-)	42	2,874	2,916
	1,391	12,494	13,885

<u>PERC RULE CHARACTERISTICS</u>
Prevalence of PE: 10% (1,391/13,885)
Sensitivity: 1,349/1,391 = 97%, 95% CI (96, 98%)
Specificity: 2,874/12,494 = 23%, 95% CI (22, 24%)
Predictive value (+) Rule: 1,349/10,969 = 12.3%, 95% CI (11.7, 12.9%)
Predictive value (-) Rule: 2,874/2,916 = 98.6%, 95% CI (98.1, 98.9%)
Likelihood Ratio (+) Rule: (1,349/1,391)/(9,620/12,494) = 1.24, 95% CI (1.18, 1.30)
Likelihood Ratio (-) Rule: (42/1,391)/(2,874/12,494) = 0.18, 95% CI (0.13, 0.23)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

21% (2,916/13,885) would be considered low risk by PERC criteria. This could potentially decrease the use of CT scans by 21%. The trade off for the decrease in resource utilization is that 1.4% (42/2,916) considered low risk by PERC would have a pulmonary embolism

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see Appendix)	☐ I ■ II ☐ III ☐ IV This would be considered a level II rule. This is a rule that has been validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other but that has not yet had an impact analysis. A level II rule can be used in a wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve.
Does the rule make clinical sense?	Yes. The criteria are those considered at increased risk for pulmonary embolism. It is important to remember that PERC is intended to be used on those with a low pretest probability of PE (gestalt < 5%). PERC should not be applied to patients at high risk for PE such as those with collagen-vascular disorders or central catheters.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	The criteria as they are described in the rule are objective elements of patient history, vital signs and physical examination findings. The parameter of “no unilateral leg swelling” may be subjective if the swelling is minimal. There was no measure of inter-rater reliability provided for this rule parameter.
Is the rule applicable to the patients in my practice?	The PERC rule is intended to apply to patients at low risk of PE. This is defined as a pretest probability (clinical gestalt) of PE of < 5%. The majority of the patients meeting PERC criteria in our population are adolescent and young adult women presenting with chest pain or shortness of breath who are taking estrogen containing contraceptives.
What are the benefits of applying the rule to my patients?	The PE rule out criteria has been found to be highly sensitive with a high negative predictive value. 21% of the patients with suspected PE could benefit by avoiding further d-dimer testing, which may yield false positive tests and the radiation and expense of diagnostic imaging.
What are the risks of applying the rule to my patients?	Using this decision rule in a low prevalence population results a posttest probability of a negative rule of 1.4%. The harm done due to missed or delayed diagnosis in these patients must be balanced with the potential benefits.

CLINICAL BOTTOM LINE

BACKGROUND: The diagnosis of pulmonary embolism is difficult to make accurately using clinical criteria. This results in increased laboratory and radiologic testing. This meta-analysis sought to validate the diagnostic accuracy of the Pulmonary Embolism Rule-out Criteria and to investigate the use of this decision rule in practice to defer the use of the d-dimer test, an oversensitive screening tool.

CLINICAL QUESTION: In adult patients with a low probability of suspected pulmonary embolism what are the rule characteristics of the Pulmonary Embolism Rule-Out Criteria (PERC Low Risk Criteria) in identifying patients with and without pulmonary embolism.

DESIGN/RISK OF BIAS: This was a well-designed meta-analysis without major validity concerns. The individual studies were of high quality. The calculation of the rule characteristics included 13,885 patients of with 1,391 (10%) had a pulmonary embolism.

PRIMARY RESULTS: The investigators found that the PERC criteria are highly sensitive (97%, 95% CI (96, 98%)) though poorly specific (23%, 95% CI (22, 24%). This may be acceptable in a screening test for a rare though important diagnosis, where the priority is a low rate of missed cases. The use of the PERC criteria could result in a reduction in resource utilization by 20%. This reduction needs to be balanced by the potential harm of missing a PE in 1.4% of the patients who meet low risk criteria. The inclusion of almost 14,000 patients resulted in precise confidence intervals.

PULMONARY EMBOLISM RULE-OUT CRITERIA
Age < 50 years
Pulse < 100 beat/minute
$Sp0_2$ > 94%
No unilateral leg swelling
No hemoptysis
No surgery or trauma within 4 weeks
No previous DVT or PE
No oral hormone (OCP) use
The PERC criteria are intended to be applied only to those with a low (< 5%) probability of PE

APPLICABILITY: This is a stage II clinical decision rule. The meta-analysis of clinical decision rule can be considered as being broadly validated including a broad spectrum of patients or in several smaller settings that differ from each other. No impact analysis was performed. The rule can be used in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve.

AUTHOR'S CONCLUSION: "In summary, our meta-analysis has demonstrated high sensitivity for the PERC rule and evidence that the rule can be used in settings of low pretest probability with confidence. The major limitation of PERC is its low but acceptable specificity."

POTENTIAL IMPACT: The PERC criteria are highly sensitive for pulmonary embolism but have a low specificity. It can be used in patients with a low pre-test probability of pulmonary embolism to defer d-dimer testing.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

RESUSCITATION

1. ALS: Intubation During Cardiac Arrest: JAMA 2018
2. ALS: Epinephrine: Pre-hospital Arrest (Adult): NEJM 2018
3. ALTE: Decision Rule Derivation: Pediatr Emerg Car. 2012
4. Basic Life Support: Compression Only CPR: Lancet 2010
5. Basic Life Support: Bystander CPR: JAMA Peds 2017
6. Basic Life Support: Pulse Palpation: Resuscitation 2009
7. Post Resuscitation: Therapeutic Hypothermia: NEJM 2015
8. Sepsis: Antibiotic Timing: Crit Care Med.2014
9. Sepsis: Dopamine vs Epinephrine: Crit Care Med. 2015
10. Sepsis: Early Goal Directed Therapy: N Engl J Med 2014
11. Sepsis: ED Identification Process: Annals EM 2017
12. Sepsis: Fluid Resuscitation Rate: JAMA. 1991
13. Sepsis: Fluid Resuscitation (Africa) N Engl J Med. 2011
14. Sepsis Fluid Resuscitation Techniques Annals EM. 2007
15. Sepsis: Lactate and Organ Failure: Acad Emer Med 2012

16. Sepsis: Lactate and Mortality: JAMA Peds 2017
17. Sepsis: NY State Sepsis Bundle Completion: JAMA 2018
18. Sepsis: Pediatric qSOFA Accuracy: Frontiers Peds 2018
19. Sepsis: Pediatric SIRS Criteria: Acad Emerg Med. 2015

ADVANCED LIFE SUPPORT: ENDOTRACHEAL INTUBATION

In pediatric in-hospital cardiac arrest, does tracheal intubation during CPR, compared to no tracheal intubation during CPR, result in an improvement in survival to hospital discharge, the rate return of spontaneous circulation (ROSC) or the proportion of patients with a favorable neurologic outcome at discharge?

Nicole Gerber, MD, Alvira Shah, MD
March 2018

Andersen LW, Raymond TT, Berg RA, Nadkarni VM, Grossestreuer AV, Kurth T, Donnino MW.

ASSOCIATION BETWEEN TRACHEAL INTUBATION DURING PEDIATRIC IN-HOSPITAL CARDIAC ARREST AND SURVIVAL.

JAMA. 2016;316 (17):1786–1797.
PubMed ID: 27701623

STUDY DEFINITIONS	
POPULATION	Inclusion: <18 years with index in-hospital cardiac arrest with 1 minute or more of chest compressions. Exclusion: 1.Patients were receiving assisted ventilation prior to arrest 2.Had an invasive airway 3.Both 1 and 2 4.Hospital visitors that arrested 5.Delivery room and NICU cardiac arrests Setting: Get With The Guidelines Resuscitation registry (GWTG-R). An American Heart Association sponsored prospective registry of 253 US and Canadian hospitals. Data collected from 1/2000-12/2014.
EXPOSURE	Tracheal intubation during cardiac arrest (Defined as insertion of a tracheal tube during the cardiac arrest event)
NO EXPOSURE	No tracheal intubation during cardiac arrest
OUTCOME	Primary Outcome: Survival to hospital discharge Secondary Outocomes 1.Return of spontaneous circulation (ROSC): Defined as no further need for chest compressions (including cardiopulmonary bypass) that was sustained for longer than 20 minutes. 2.Neurologic outcome at hospital discharge: defined as a Pediatric Cerebral Performance Category Score of 1 (no neurologic disability) or 2 (moderate disability) or no increase from baseline. See Appendix
DESIGN	Retrospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	Yes (Table 1). There were differences in the intubation and no intubation group in terms of illness category (medical vs. surgical), location of arrest (Floor vs. ED vs. ICU), year of arrest (with trends towards less intubation over time), whether the arrest was witnessed, whether the patient was monitored at the onset of the event, when the patient became pulseless, whether the initial rhythm was shockable and the teaching status of the hospital. To account for this, most of the analyses performed by the authors used propensity score matching, a statistical technique to try to estimate the effect of the intervention by accounting for the covariates that predict receiving the intervention (in this case tracheal intubation). The co-variates that they accounted for included: gender, age group, pre-existing conditions, time of week, time of day, whether the cardiac arrest was witnessed and/or monitored. They found Admission diagnosis, arrest location, type of hospital and year of arrest to not be significant so those co-variates were excluded from the model. Their matched sample for their main analyses is presented in Table 2, and the patients appear to be well matched on all of the characteristics.
Were the circumstances and methods for detecting the outcome similar?	Yes. All of the data used for their analyses comes from the GWTG-R registry. Data is entered into the registry by certified trained research coordinators at each institution who abstract the data from the hospital medial records
Was follow-up sufficiently complete?	537 patients (19%) had missing or inconsistent data on tracheal intubation, timing of intubation, timing of the end of resuscitation, and timing of pulselessness, survival or relevant co-variates. These patients were excluded from the majority of analyses, but were included in a preplanned sensitivity analysis. 414 patients (18%) had missing data on neurologic outcomes at hospital discharge.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

Demographic Data
N= 2,294, Median Age: 7 months
Intubated: 1555 (67.8%), Not Intubated: 739 (32.2%)
Median time to successful intubation from start of chest compressions: 5 minutes
Survival to hospital discharge: 1162 (51%)
ROSC 1766 (77%)
Favorable neurologic outcome: 557/748 survivors (74%)

Primary Outcome: Time Dependent Propensity Matched Multivariable Analyses (N = 2,270)
Secondary Analyses:

OUTCOME	INTUBATED	NOT INTUBATED	RR (95% CI)	P-VALUE
Survival to Hospital Discharge	411/1135 (36%)	460/1135 (41%)	0.89 (0.81, 0.99)	.03
Return of Spontaneous Circulation	770/1135 (68%)	771/1135 (68%)	1.00 (0.95, 1.06)	.96
Neurologically Favorable Outcome	185/987 (19%)	211/983 (21%)	0.87 (0.75, 1.02)	.08

1. Unadjusted Analyses: Tracheal intubation was associated with decreased survival to hospital discharge, decreased ROSC and decreased favorable neurological outcome
2. Time-Dependent Propensity-Matched Multivariable Analyses (See above table)
   Including sensitivity analysis for an unmeasured confounder and a traditional not time-dependent propensity score-matched analysis
3. Timing of intubation: Association between tracheal intubation and survival did not change with the duration of the cardiac arrest
4. Sensitivity Analysis accounting for missing data: Included 2831 patients. Created 10 imputed data sets and did combined estimates. Tracheal intubation associated with decreased survival and decreased favorable neurologic outcome. No association with ROSC.
5. Extracorporeal CPR (E-CPR): 111 (5%) of patients received E-CPR. Excluding those patients they had 2181 patients, 2116 were matched for the analysis. Tracheal intubation was associated with decreased survival and not associated with the secondary outcomes.
6. Only patients receiving 2 minutes or more of CPR: Including only patients with 2 minutes or more of chest compressions and excluding patients intubated 2 min or less after the start of chest compressions they matched 1762 patients. Tracheal intubation was associated with decreased survival. Not associated with the secondary outcomes.
7. Only patients who had documented pulselessness: Sub-analysis of only patients who lost a pulse at any time during the event. 1494 patients included. 1019 (68%) were intubated. Overall survival was 40%. 1,706 patients were matched for analysis. Tracheal intubation was not associated with any of the outcomes.
8. Only patients who started the event with a pulse (i.e. severe bradycardia): 935 patients. 66% survival to hospital discharge. 223 (24%) lost their pulse during the resuscitation. 573 (61%) were intubated. 650 patients matched for analysis. Tracheal intubation was associated with decreased survival and decreased favorable neurologic outcome. Not associated with ROSC.

HOW PRECISE IS THE ESTIMATE OF THE RISK?

For all of the outcomes from the main time-dependent propensity matched multivariable analysis, because the database is so large, the confidence intervals are narrow.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Yes. The GWTG-R is a large American Heart Association sponsored registry with participating hospitals across the United States.
Was follow-up sufficiently long?	One of the limitations of this study is that there is no long term follow up of the survivors. The outcomes included is only: survival to hospital discharge, ROSC with no need for chest compressions for longer than 20 minutes and neurological outcome at discharge. Whiles these are accepted markers for successful resuscitation they do not provide information on long term outcomes.
Is the exposure similar to what might occur in my patient?	In this population, only around 68% of patients were intubated during their cardiac arrest. We likely have a higher rate of intubation.
What is the magnitude of the risk?	Intubation during CPR was associated with a small but statistically significant decrease in survival to hospital discharge (Absolute Risk Difference: 41% - 36% = 5%). without any association with ROSC or neurologically favorable outcome at hospital discharge.
Are there any benefits that offset the risks associated with exposure?	Intubation may result in delay of chest compressions or other interventions like defibrillation. It may pull away the team leader if they are the most experienced person and perform the intubation. In addition, intubation may result in hyperventilation and increased intrathoracic pressure. In some cases, if the tube is malpositioned, it may go unrecognized leading to poor oxygenation and ventilation.

CLINICAL BOTTOM LINE

BACKGROUND: Mortality from pediatric in hospital cardiac arrest remains high. Since most pediatric cardiac arrests are related to respiratory failure, CPR focuses on early intubation. However, intubation can be challenging and is not without risk. Based on the available evidence, tracheal intubation is currently not recommended for pediatric out of hospital cardiac arrest if there is a short transport time (Gausche, JAMA. 2000 PubMed ID: 10683058, Ohashi-Fukuda, Resuscitation 2017, PubMed ID: 28267617). There is little evidence on importance intubation for pediatric in-hospital cardiac arrest. This article set out to find out if tracheal intubation during cardiac arrest was associated with improved survival to hospital discharge.

CLINICAL QUESTION: In pediatric in hospital cardiac arrest, does tracheal intubation during CPR, compared to no tracheal intubation during CPR, result in any change in survival to hospital discharge, return of spontaneous circulation (ROSC) or neurologic outcome at discharge?

DESIGN/RISK OF BIAS: This is a well-designed retrospective cohort study from a large database with 2294 pediatric patients with in-hospital cardiac arrest. The Get With the Guidelines Resuscitation registry (GWTG-R) is a large registry of 253 US and Canadian hospitals containing cardiac arrest data collected by specially trained certified research coordinators. There are minimal validity concerns given the size of the cohort and the standardized methods used to obtain information for the database. The authors used time dependent propensity matching to account for many of the potential confounders or the study outcomes. ,However, data was missing on 18% of patients. In addition, as this is an observational study, there may have been unmeasured confounders, as the registry does not have data on many important clinical considerations such as the specific indication for intubation, clinician experience and background, quality of the CPR, effectiveness of noninvasive oxygenation and ventilation, number of intubation attempts and post-ROSC care.

The primary outcome was survival to hospital discharge, with the secondary outcomes being ROSC defined as no further need for chest compressions sustained for longer than 20 minutes, and neurological outcome at discharge defined as a Pediatric Cerebral Performance Category Score of 1 (no neurologic disability) or 2 (moderate disability) or no increase from baseline.

PRIMARY RESULTS: Of the 2,294 patients, 67.8% of patients were intubated and 32.2% were not. In the primary time dependent propensity matching analysis tracheal intubation was associated with a decreased survival to hospital discharge (RR: 0.89, 95% CI (0.81-0.99). There was no association with either of the secondary outcomes, ROSC (RR: 1.00, 95% CI (0.95-1.06) or neurologically favorable outcome at hospital discharge (RR: 0.87, 95% CI (0.75-1.02). The authors also employed multiple statistical techniques to account for the timing of intubation, missing data, E-CPR, patients receiving only ≥ 2 minutes of CPR, patients with documented pulselessness and patients who started the event with a pulse. In all of the sub-analyses, except when only looking at patients with documented pulselessness, tracheal intubation was associated with decreased survival to hospital discharge.

APPLICABILITY: Although the GWTG-R registry only allows for a retrospective cohort study to be performed to answer the question on the association of tracheal intubation during CPR and survival to hospital discharge, the authors employed multiple statistical techniques to make their results meaningful. This information is likely applicable to our pediatric patients who undergo in-hospital cardiac arrest.

AUTHOR'S CONCLUSION: "Among pediatric patients with in-hospital cardiac arrest, tracheal intubation during cardiac arrest compared with no intubation was associated with decreased survival to hospital discharge. Although the study design does not eliminate the potential for confounding, these findings do not support the current emphasis on early tracheal intubation for pediatric in-hospital cardiac arrest."

POTENTIAL IMPACT: This study is currently the best evidence available on the association of tracheal intubation during CPR with survival to hospital discharge. This study highlights that although tracheal intubation is performed in the majority of pediatric patients undergoing in-hospital cardiac arrest, it may not be the most important factor in successful resuscitation. However, it is important to remember that endotracheal intubation may be the only acceptable intervention in the pediatric patient with upper airway obstruction (e.g. severe croup, bacterial tracheitis, epiglottitis, anaphylaxis and smoke inhalation). In these situations, a delay in intubation can lead to an inability to ventilate the patients.

APPENDIX: CEREBRAL PERFORMANCE CATEGORY SCALE

CEREBRAL PERFORMANCE CATEGORY SCALE	
1	Full recovery or mild disability
2	Moderate disability but independent activities of daily living
3	Severe disability, dependent in activities of daily living
4	Persistent vegetative state
5	Dead

ADVANCED LIFE SUPPORT:
EPINEPHRINE FOR PRE-HOSPITAL ARREST (ADULT)

In adult patients with out-of-hospital cardiac arrest does Epinephrine when compared to Placebo improve survival at 30 days?

Michael Mojica, MD
August 2018

Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scomparin C, Regan S, Long J, Slowther A, Pocock H, Black JJM, Moore F, Fothergill RT, Rees N, O'Shea L, Docherty M, Gunson I, Han K, Charlton K, Finn J, Petrou S, Stallard N, Gates S, Lall R. (PARAMEDIC2 Trial: Prehospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest)

A RANDOMIZED TRIAL OF EPINEPHRINE IN OUT-OF-HOSPITAL CARDIAC ARREST

N Engl J Med. 2018 Jul 18.
PubMed ID: 30021076

STUDY DEFINITIONS	
POPULATION	Inclusion: Adults, out of hospital cardiac arrest, advanced life support by paramedics, initial resuscitation attempts (CPR, defibrillation) unsuccessful Exclusion: Pregnancy, age < 16 years, arrest from anaphylaxis or asthma, Epinephrine administered prior to paramedic arrival, traumatic cardiac arrest (1 of the 5 ambulance services) Setting: 5 national health service ambulance services in the United Kingdom, 12/2014-10/2017
INTERVENTION	Epinephrine 1 mg IV/IO, Q3-5 minutes
CONTROL	Placebo (0.9% saline) IV/IO, Q3-5 minutes
CO-INTERVENTIONS	European Resuscitation Guideline protocols followed. Treatment continued until: 1. Sustained pulse 2. Resuscitation discontinued (followed clear criteria for discontinuation) 3. Care transferred to hospital
OUTCOME	Primary Outcome: Survival at 30 days Secondary Outcomes: 1. Survival to hospital admission and hospital discharge 2. Length of stay in hospital and ICU 3. Survival at 90 days 4. Neurologic outcomes at hospital discharge and 3 months: Favorable neurologic outcomes defined as a modified Rankin score ≤ 3 Severe neurologic outcomes defined as a modified Rankin score of 4-5 Modified Rankin Score (0= No symptoms, 6 = Death), See Appendix
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Randomization was computer generated with an assignment ratio of 1:1
Was randomization concealed?	Yes. The authors state that the “programing team provided randomization and concealed assignment.” Identical trial packs with 10 prefilled syringes were provided.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Patients were similar with regard to demographic characteristics (Table 1) as well as concurrent treatments (Table S1) and time until ambulance arrival and treatment (Table 2).
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Yes. Paramedic caregivers and outcomes assessors were blinded to treatment assignment.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Only a few patients were lost to follow up (Figure 1).

LOST TO FOLLOW-UP		
	Survival Analysis	Neurologic Analysis
Placebo	8/3,999 (0.2%)	20/3,999 (0.5%)
Epinephrine	6/4,015 (0.1%)	29/4,015 (0.7%)

Were patients analyzed in the groups to which they were randomized?	Unclear. The primary analysis was described as a modified intention to treat analysis. This included all patients who underwent randomization and received the assigned interventions. This definition appears to be that of a per protocol analysis. 3,995/3,999 (99.9%) randomized to the Placebo group and 4,012/4,015 (99.9%) randomized to the Epinephrine group were included in the primary analysis. Therefore, there is likely no difference between the results of the intention to treat and the per protocol analysis.
Was the trial stopped early?	No. The trial was not stopped early. A sample size of 8,000 patients was required for a risk difference of 1.5% (relative risk of 1.25) in the primary outcome based on 30-day survival of 6.0% in the placebo group and 7.5% in the epinephrine group. 8,014 patients were included in the primary analysis.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 8,014 (Epinephrine: 4,015, Placebo: 3,999)

TIME INTERVALS (MINUTES) AND RESPONSE	EPINEPHRINE	PLACEBO
Call to ambulance arrival (median, IQR)	6.7 (4.3, 9.7)	6.6 (4.2, 9.6)
Call to administration of trial agent (median, IQR)	21.5 (16.0, 27.3)	21.1 (16.1, 27.4)
Ambulance arrival and scene departure (mean ± SD)	50.1 ± 21.8	44.5 ± 18.3
Ambulance departure and hospital arrival (mean ± SD)	12.9 ± 9.8	12.4 ± 8.9
Initiation of ALS to cessation (median, IQR)	47.5 (35.1, 64.0)	43.1 (33.5, 56.1)
Return of Spontaneous Circulation (ROSC) (%)	36.3%	11.7%
Transported to hospital (%)	50.8%	30.7%
Death declared in ED (%)	24.6%	17.2%

PRIMARY AND SECONDARY SURVIVAL OUTCOMES				
OUTCOME	EPINEPHRINE	PLACEBO	RISK DIFFERENCE[1]	ADJUSTED OR
Survival to Admit	947/3,973 (23.8%)	319/3,982 (8.0%)	15.8% (14.3, 17.4%)	3.83 (3.30, 4.43)
Survival 30 days	130/4,012 (3.2%)	94/3,995 (2.4%)	0.9% (0.2, 1.6%)[2]	1.47 (1.09, 1.97)
Survival to D/C	128/4,009 (3.2%)	91/3,995 (2.3%)	0.9% (0.2, 1.6%)	1.48 (1.10, 2.00)
Survival 90 days	121/4,009 (3.0%)	86/3,991 (2.2%)	0.9% (0.2, 1.6%)	1.47 (1.08, 2.00)

GREEN = Statistically Significant, RED = Not Statistically Significant

1. Risk differences were not presented. Calculated at the Centre for EBM Website (WEB LINK)
2. The authors considered a 1.5% difference in the primary outcome to be clinically significant in their sample size determination. A 0.9% difference, though statistically significant, would not be clinically significant by the author's criteria.

In the subgroup analyses, there was no modification of the treatment effect by: patient age, whether the cardiac arrest was witnessed, whether CPR was performed by a bystander, initial cardiac rhythm, ambulance response time or time to trial-agent administration.

It is unclear why the proportion of patients at hospital discharge with a favorable neurologic outcome (MRS ≤ 3) used a denominator of total patients (MRS 0-6) and while the proportion with severe neurologic impairment (MRS = 4-5) at hospital discharge uses a denominator of patients who survived not including those who died (MRS 0-5). Neurologic outcomes are calculated in the table below using each of the different denominators for direct comparison. In patients who survived to hospital discharge the Epinephrine group were more likely to have severe neurologic outcomes.

NEUROLOGIC OUTCOMES				
OUTCOME	EPINEPHRINE	PLACEBO	RISK DIFFERENCE[1]	ADJUSTED OR
Favorable at D/C[3]	87/4,007 (2.2%)	74/3,994 (1.9%)	0.3% (-0.03, 0.9%)	1.19 (0.85, 1.68)
Severe at D/C[3]	39/4,007 (9.7%)	16/3,994 (0.04%)	0.6% (0.2, 1%)	2.43(1.36, 4,34)[2]
Favorable at D/C[4]	87/126 (69.0%)	74/90 (82.2%)	-13.2% (1.4, 23.9%)	0.84(0.77, 0.97)[2]
Severe at D/C[4]	39/126 (31.0%)	16/90 (17.8%)	13.2% (0.1, 23.9%)	1.74(1.04, 2.91)[2]

GREEN = Statistically Significant, RED = Not Statistically Significant

1. Risk differences were not presented. Calculated at the Centre for EBM Website (WEB LINK)
2. Adjusted odds ratios not provided for this outcome. These are calculated unadjusted relative risks
3. Denominator is all patients (Modified Rankin Score = 0-6)
4. Denominator is patients who survived to hospital discharge (Modified Rankin Score = 0-5)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See confidence intervals for the risk differences and odds ratios above.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Unclear. These were patient from both rural and urban areas of the U.K. so there may be some differences from a US population. In particular, the proportion of patients presenting with a toxicologic arrest was less than 2% of the study population. In addition, the time from ambulance arrival to scene departure averaged over 44 minutes. This is significantly higher than our time at the scene.
Were all patient important outcomes considered?	Yes. Both survival and the modified Rankin scale which provides a measure of the ability to carry out daily activities would be important to patients.
Are the likely treatment benefits worth the potential harm and costs?	The number needed to treat for survival at 30 days is 111 (1/ARD = 1/0.009). For every 111 patients treated with Epinephrine, 1 additional patient would survive to 30 days. The authors presented the results for favorable and severe outcomes using different denominator making comparison difficult. The table below present the number needed to harm (NNH) for both outcomes using both of the different denominators used.

NEURO OUTCOME	NUMERATOR	DENOMINATOR	RISK DIFFERENCE	NNT/NNH
Favorable at D/C	MRS ≤ 3	MRS = 0-6	0.3% (-0.03, 0.9%)	333*
Severe at D/C	MRS = 4 or 5	MRS = 0-6	0.6% (0.2, 1%)	167
Favorable at D/C	MRS ≤ 3	MRS = 0-5	-13.2% (1.4, 23.9%)	8
Severe at D/C	MRS = 4 or 5	MRS = 0-5	13.2% (0.1, 23.9%)	8

GREEN = Statistically Significant, RED = Not Statistically Significant

*NNT/NNH is typically not calculated for risk differences that are not statistically significant. It is presented here only for comparison to the number need to harm for severe neurologic outcomes at hospital discharge

CLINICAL BOTTOM LINE

BACKGROUND: The efficacy of defibrillation in adult out-of-hospital cardiac arrest with a shockable rhythm is well established. The efficacy of medications in those with and without a shockable rhythms is less well established. Epinephrine is recommended in resuscitation guidelines for pulseless ventricular tachycardia, ventricular fibrillation, pulseless electrical activity and asystole. There is good evidence that Epinephrine improves the rate of return of spontaneous circulation but limited evidence that it is associated with improved survival and in particular neurologically favorable survival.

CLINICAL QUESTION: In adult patients with out-of-hospital cardiac arrest does Epinephrine when compared to Placebo improve survival at 30 days?

DESIGN/VALIDITY: This was a well-designed randomized clinical trial without significant risk of bias. The trial was conducted in 5 national health service ambulance services in the United Kingdom. Patients were randomized to either Epinephrine 1 mg IV/IO, Q3-5 minutes or Placebo (0.9% saline) IV/IO, Q3-5 minutes. Non-trial management was based on European resuscitation guidelines.

The primary outcome was survival at 30 days. Secondary Outcomes included: survival to hospital admission: hospital and ICU length of stay, survival at 90 days and neurologic outcomes at hospital discharge and 3 months. A favorable neurologic outcome was defined as a score of ≤ 3 on the modified Rankin scale. Patients were similar with regard to regard to demographic characteristics (Table 1), concurrent treatments (Table S1) and time until ambulance arrival (Table 2). There were very few patients lost to follow up. Both regression and subgroup analyses were conducted.

The primary risk of bias is that in-hospital interventions were not included as potential confounders. In addition, information on the quality of CPR performed was only available in 5% of patients and only for 5 minutes. It is unclear why traumatic cardiac arrest was included though less than 2% of patients had a traumatic cardiac arrest

PRIMARY RESULTS: 8,014 patients were included (Epinephrine: 4,015, Placebo: 3,999). Return of spontaneous circulation was more common in the Epinephrine group (36.3%) than the Placebo group (11.7%)(Risk Difference: 24.6%, 95% CI(22.8, 26.4). Patients in the Epinephrine group were statistically more likely to survive until hospital admission, hospital discharge, 30 days and 90 days (Table below). The low rate of survival in this study can likely be attributed to the fact that those that initially responded to CPR and/or defibrillation were excluded from the study.

PRIMARY AND SECONDARY SURVIVAL OUTCOMES

OUTCOME	EPINEPHRINE	PLACEBO	RISK DIFFERENCE[1]	ADJUSTED OR
Survival to Admit	947/3,973 (23.8%)	319/3,982 (8.0%)	15.8% (14.3, 17.4%)	3.83 (3.30, 4.43)
Survival 30 days	130/4,012 (3.2%)	94/3,995 (2.4%)	0.9% (0.2, 1.6%)[2]	1.47 (1.09, 1.97)
Survival to D/C	128/4,009 (3.2%)	91/3,995 (2.3%)	0.9% (0.2, 1.6%)	1.48 (1.10, 2.00)
Survival 90 days	121/4,009 (3.0%)	86/3,991 (2.2%)	0.9% (0.2, 1.6%)	1.47 (1.08, 2.00)

GREEN = Statistically Significant, RED = Not Statistically Significant

1. Risk differences were not presented. Calculated at the Centre for EBM Website (WEB LINK)
2. The authors considered a 1.5% difference in the primary outcome to be clinically significant in their sample size determination. A 0.9% difference though statistically significant would not be clinically significant by the author's criteria.

It is unclear why the proportion of patients at hospital discharge with a favorable neurologic outcome (MRS ≤ 3) used a denominator of total patients in each group (MRS 0-6) while the proportion with severe neurologic impairment (MRS = 4-5) at hospital discharge uses a denominator of patients who survived to discharge excluding those who died (MRS 0-5). Neurologic outcomes are calculated in the table below using both of the denominators for comparison. In patients who survived to hospital discharge the Epinephrine group were more likely to have severe neurologic outcomes.

NEUROLOGIC OUTCOMES				
OUTCOME	EPINEPHRINE	PLACEBO	RISK DIFFERENCE[1]	ADJUSTED OR
Favorable at D/C[3]	87/4,007 (2.2%)	74/3,994 (1.9%)	0.3% (-0.03, 0.9%)	1.19 (0.85, 1.68)
Severe at D/C[3]	39/4,007 (9.7%)	16/3,994 (0.04%)	0.6% (0.2, 1%)	2.43(1.36, 4,34)[2]
Favorable at D/C[4]	87/126 (69.0%)	74/90 (82.2%)	-13.2% (1.4, 23.9%)	0.84(0.77, 0.97)[2]
Severe at D/C[4]	39/126 (31.0%)	16/90 (17.8%)	13.2% (0.1, 23.9%)	1.74(1.04, 2.91)[2]

GREEN = Statistically Significant, RED = Not Statistically Significant
1. Risk differences were not presented. Calculated at the Centre for EBM Website (WEB LINK)
2. Adjusted odds ratios not provided for this outcome. These are calculated unadjusted relative risks
3. Denominator is all patients (Modified Rankin Score = 0-6)
4. Denominator is patients who survived to hospital discharge (Modified Rankin Score = 0-5)

APPLICABILITY: These were patient from both rural and urban U.K. There may be some differences from a U.S. population. In particular, the proportion of patients presenting with a toxicologic arrest was less than 2% of the study population. In addition, the time from ambulance arrival and scene departure average was over 44 minutes. This is a significantly higher time at scene than our EMS system, which adheres to a “scoop and run” rather than a “stay and play” approach.

The number needed to treat for survival at 30 days is 111 (1/ARD = 1/0.009). For every 111 patients treated with Epinephrine, 1 additional patient would survive to 30 days. For comparison, the NNT is much lower for early defibrillation (NNT=5), early recognition of cardiac arrest (NNT=11) and bystander CPR (NNT=15)(note: non-study data). The number needed to harm (NNH) for severe neurologic outcome at hospital discharge is dependent on the denominator used to calculate the risk difference. The NNH using a denominator of all patients is 167. For every 167 patients treated with Epinephrine, 1 additional patient would have a severe neurologic outcome. The NNH using only patients who survived to hospital discharge is 8. For every 8 patients treated with Epinephrine who survived to hospital discharge, 1 additional patient would have a severe neurologic outcome.

AUTHOR’S CONCLUSION: “In conclusion, in this randomized trial involving patients with out-of-hospital cardiac arrest, the use of epinephrine resulted in a significantly higher rate of survival at 30 days than the use of placebo, but there was no significant between-group difference in the rate of a favorable neurologic outcome because more survivors had severe neurologic impairment in the epinephrine group.”

POTENTIAL IMPACT: This was a well-designed, placebo controlled, blinded randomized clinical trial that assessed important clinical outcomes. The use of Epinephrine when compared to Placebo for adult out of hospital cardiac arrest resulted in a statistically significant increase in survival at 30 days (3.2% vs 2.4%, risk difference 0.9% (0.2, 1.6%). The clinical significance of this difference is unclear. The increase in survival should be weighed against an increased rate of severe neurologic outcomes in patients who survived to hospital discharge in the Epinephrine group. Whether this study's results should change clinical care in the Emergency Department is unclear. It will be interesting to see if the 2020 revisions of the American Heart Association Guidelines will incorporate the study's results.

APPENDIX: MODIFIED RANKIN SCALE

MODIFIED RANKIN SCALE		
0	No symptoms at all	
1	No significant disability	Despite symptoms, is able to carry out all usual duties and activities
2	Slight disability	Unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability	Requiring some help, but able to walk without assistance
4	Moderately severe disability	Unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability	Bedridden, incontinent and requiring constant nursing care and attention
6	Dead	

APPARENT LIFE-THREATENING EVENT: DECISION RULE DERIVATION

In infants with an apparent life-threatening event can history and physical examination parameters identify those who are at low risk of requiring significant interventions?

Alvira Shah, M.D., Seema Awatramani, M.D.
June 2013

Mittal MK, Sun G, Baren JM.

A CLINICAL DECISION RULE TO IDENTIFY INFANTS WITH APPARENT LIFE-THREATENING EVENT WHO CAN BE SAFELY DISCHARGED FROM THE EMERGENCY DEPARTMENT.

Pediatr Emerg Care. 2012 Jul;28(7):599-605.
PubMed: 22743742

STUDY DEFINITIONS	
POPULATION	Inclusion: < 12 months, meeting NIH criteria for ALTE, confirmed by ED attending physician or pediatric emergency medicine fellow Exclusion: Clear evidence of a definite disease such as febrile seizure or bronchiolitis on ED Setting: Single Children's Hospital ED, 6/2006-1/2008
RULE PARAMETERS	Standardized interview of parents: Demographic data and history Physical exam by ED faculty or fellow Review in records for admitted patients Structured phone follow up at 4 weeks (99.3% follow up obtained)
REFERENCE STANDARDS	Significant Interventions Cardiology evaluation and echocardiogram Abnormal pneumogram leading to discharge on an apnea monitor Repeat ALTE requiring intervention by healthcare provider to terminate it ICU admission Hypoxia: SaO_2 < 95% requiring oxygen Antibiotics for confirmed serious bacterial infection Intubation Repeated airway suctioning Abnormal EEG leading to the prescription of an antiepileptic Death during hospitalization or within 72 hours of discharge Other major illness
OUTCOME	1. Admitted patients: Any significant intervention during admission 2. Discharged patients: Recurrence of ALTE resulting in repeat ED visit, death or any major event within 72 hours
DESIGN	Observational: Prospective cohort:

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. Predictors assessed are listed in Table 1: Characteristics of study cohort and Table 2: Characteristics of the ALTE. Previous studies have identified prematurity, age < 30 days or > 60 days, History of other illness, recurrent ALTE, and abnormal result on the initial exam as predictors. This study did not look at age or other chronic illnesses such as cardiac disease.
Were all important predictors present in significant proportion of the study population?	The proportion of patients with an abnormal physical examination was not presented. Of the other 4 predictors the predictors with the lower prevalence was prematurity with a prevalence of 33%.
Were the outcome event and predictors clearly defined?	Yes. Table 5 shows Predictors of significant interventions. Table 4 lists the significant interventions/events during hospitalization and after discharge.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	No. Research assistants screened patients during the day and MDs enrolled/examined infants at night. Those involved in this study would know what the infants' history and physical examination findings were and would be aware if significant intervention was required in ED.
Was the sample size adequate (including an adequate number of outcome events)?	In general, logistic regression requires 10 outcomes for each predictor included in the rule. The requirements for recursive partitioning are unclear. Both methods were applied in this study. The rule included 5 predictors so 50 interventions would be required. 37 interventions were included.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? How precise was this measurement? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

300 infants with ALTE
37 (12.3%) required 72 significant interventions
Mean age: 50 days, 33% premature
Admission: 76%
Discharge diagnosis: Reflux 49%, viral infection 18.7%, 35.7% no other diagnosis than ALTE, 0% SBI

REGRESSION: PREDICTORS	ADJUSTED ODDS RATIO (95% CI)
Prematurity	4.5 (2.0, 9.9)
Abnormal examination in ED	3.4 (1.5, 7.5)
Color change to cyanosis	3.2 (1.4, 7.2)
No History URI in past 24 hours	2.9 (1.1, 7.9)
No History choking	2.3 (1.1, 1.5)

Regression Rule Characteristics
Prevalence: 12%
Sensitivity: 97.1%, 95% CI (85.5, 99.5%)
Specificity: 6.4%, 95% CI (4, 10.1%)
Predictive value (-) Rule: 94.1%, 95% CI (73, 99%)
Predictive value (+) Rule: 12.6%, 95% CI (9.2, 17.1%)

Recursive Partitioning: Low risk infants (See Appendix)
1. Full term without cyanosis
2. Full term with cyanosis with choking with normal exam
3. Preterm with URI symptoms

Recursive Partitioning Characteristics
Prevalence: 12.2%
Sensitivity: 80%, 95% CI (64.1, 90%)
Specificity: 70.5%, 95% CI (64.6, 75.8%)
Predictive value (-) Rule: 96.2%, 95% CI (92.4, 98.1%)
Predictive value (+) Rule: 27.5%, 95% CI (19.7, 36.8%)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

184/286 (64%) were identified as rule negative. If all rule negative patients were discharged home, there is 64% potential decrease in resource utilization (admission). In the study population, using the rule, 36% of the infants would be admitted compared to the 76% before use of the rule. Therefore, there would be 40% less hospitalization.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

There was an internal cross validation analysis. The validation data set had similar rule characteristics.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see Appendix)	☐ I ☐ II ☐ III ■ IV This is a level 4 CDR. The rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. Level IV rules require further validation before it can be applied clinically.
Does the rule make clinical sense?	Using this CDR would help decrease admissions but you would also miss patients who needed further interventions and could potentially have detrimental outcomes. I would also consider social history as part of my admission criteria. If I felt the parents could not monitor the baby or follow up with their primary care provider then I'd be more likely to admit.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	The rule was derived at single institution that is a major referral center potentially limiting generalizability due to referral bias. The clinical decision tree is easy to follow. There is some concern for subjective interpretation of the rule parameters of 'upper respiratory infection' and 'choking'. It would have helped to have measured inter-rater reliability of these parameters. Specific definitions of these parameters should be included with the algorithm.
Is the rule applicable to the patients in my practice?	This study was conducted at a single children's hospital. Patient characteristics, discharge diagnosis, admission rate, and rate of significant intervention were similar to those in other studies. The prevalence of ALTE is 1% of ED visits for infants, which is also similar to other studies. This study had a high proportion of preterm infants (34%; national is 12.3%).
Will the rule results change my management strategy?	No. The rule requires further validation before it can be applied clinically.
What are the benefits of applying the rule to my patients?	The rule has the potential to decrease hospitalization, decrease unnecessary labs/imaging, decrease parental fear/ anxiety, decrease exposure of infant to nosocomial infections.
What are the risks of applying the rule to my patients?	The risk of applying the rule is the potential ins discharging an infant from the ED who required further evaluation and interventions and who may have a more significant event at home after discharge.

CLINICAL BOTTOM LINE

BACKGROUND: An ALTE or apparent life-threatening event is an episode that is frightening to the observer and that is characterized by some combination of:
1. Apnea (central or occasionally obstructive)
2. Color change (usually cyanotic or pallid but occasionally erythematous or plethoric)
3. Change in muscle tone (usually marked limpness/hypotonia) or
4. Choking, or gagging.

ALTE is constellation of symptoms and not a diagnosis. Most studies have found the natural history of ALTE to be benign though a few infants may have a life-threatening condition. There is considerable variability in who is admitted and the extent of the diagnostic evaluation conducted. The ability to determine which infants who are low risk for poor outcomes would be valuable.

CLINICAL QUESTION: In infants with an apparent life-threatening event can history and physical examination parameters identify those who are at low risk of requiring significant interventions?

DESIGN/RISK OF BIAS: This was prospective cohort study including 300 infants with ALTE of which 37 (12.3%) required 72 significant interventions. Predictors for significant intervention were identified in infants admitted for ALTE. These were used to derive a clinical decision rule to identify infants with ALTE who are at low risk of adverse outcome and can be discharged home safely from the ED.

PRIMARY RESULTS: Rule parameters identified were: Gestational age (term vs preterm), color change (blue vs not blue), choking (yes or no), exam (normal vs abnormal) and upper respiratory symptoms (yes vs no). Low risk infants were those who were:
1. Full term without cyanosis OR
2. Full term with cyanosis with choking and a normal examination OR
3. Preterm with URI symptoms

The sensitivity of the rule is 80%, 95% CI (67, 93%) and the predictive value of a negative rule is 96.2%, 95% CI (92, 98.3%). The rule stratified the patients with an overall rate of 12.3% requiring intervention into a low risk group (3.8% requiring intervention) and a high-risk group (28% requiring intervention). The specificity of the rule was 70.5 %, 95% CI (64.4, 76%).

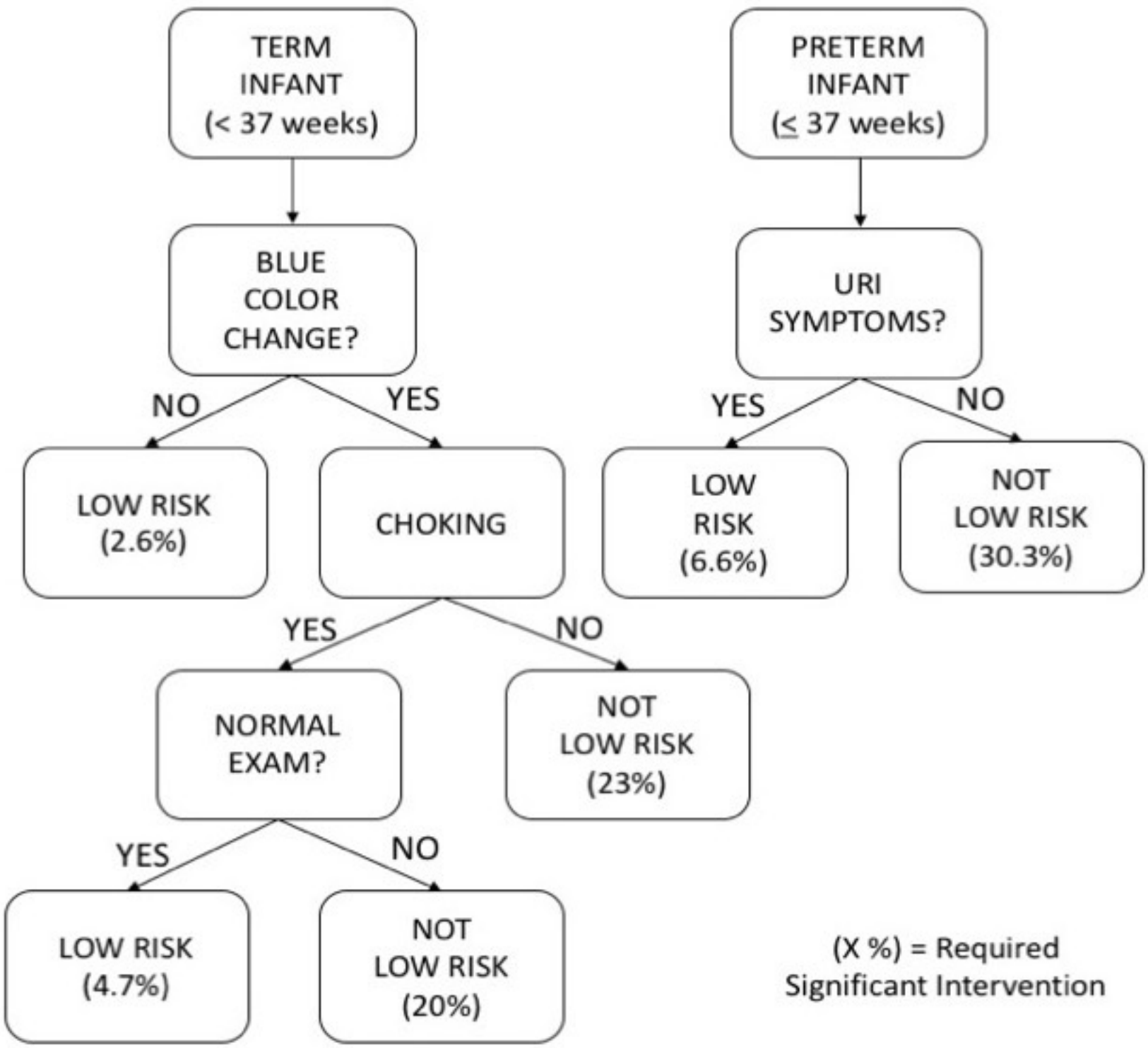
On the basis of the rule 184 infants (64%) were considered rule negative and could potentially be safely discharged from the ED. The study's discharge rate was 24%. Using of the rule to determine disposition would have would increased the discharge rate by 40%. However, the rule misclassified 7 of the 35 infants who required a significant intervention in the hospital as low risk.

APPLICABILITY: The study was conducted at a major children's hospital potentially resulting in referral bias and limiting the generalizability of the rule to other settings. The interpretation of some of the rule parameters is subjective and inter-rater reliability was not assessed. This rule is a Level IV decision rule. Level IV rules require further validation before they can be applied clinically.

AUTHOR'S CONCLUSION: "Only 12% of infants presenting to the ED with ALTE had a significant intervention warranting hospital admission. We created a CDR that would have decreased the admission rate safely by 40% from 76% (observed) to 36%. It would be useful to validate it through larger multicenter studies before implementation in routine practice."

POTENTIAL IMPACT: This is one of the largest prospective studies on infants presenting to ED with ALTE. Further validation is required before it could be applied clinically. New Guidelines for Brief Resolved Unexplained Events (BRUE) has remove a subset of traditional ALTE patients from the mix requiring the derivation of a new clinical decision rule for those patients excluded because of a BRUE.

APPENDIX: STUDY DECISION TREE



BASIC LIFE SUPPORT:
COMPRESSION ONLY CPR

In out-of-hospital pediatric cardiac arrest in which bystanders initiate CPR does chest compression only CPR when compared to standard CPR (chest compressions and rescue breathing) result in improved neurologic outcomes at 1 month?

David Kessler, M.D., Kevin Ching, M.D.
October 2009

Kitamura T, Iwami T, Kawamura T, Nagao K, Tanaka H, Nadkarni VM, Berg RA, Hiraide A; I Implementation working group for All-Japan Utstein Registry of the Fire and Disaster Management Agency.

CONVENTIONAL AND CHEST-COMPRESSION-ONLY CARDIOPULMONARY RESUSCITATION BY BYSTANDERS FOR CHILDREN WHO HAVE OUT-OF-HOSPITAL CARDIAC ARRESTS: A PROSPECTIVE, NATIONWIDE, POPULATION-BASED COHORT STUDY.

Lancet. 2010 Apr 17;375(9723):1347-54.
PubMed ID: 20202679

STUDY DEFINITIONS	
POPULATION	Inclusion: ≤17 years, out-of-hospital cardiac arrest, treated by emergency medical service (EMS) personnel and transported to medical institutions Exclusion: Arrests occurred after arrival of EMS, witness status was not documented. Setting: All-Japan Utstein registry of the Fire and Disaster Management Agency (FDMA). A prospective, nationwide, population-based registry system of out-of-hospital cardiac arrests in adults and children, 1/2005-12/2007
EXPOSURE A	Chest compression only CPR Conventional (Chest compression and rescue breathing) CPR
EXPOSURE B	No Bystander CPR Any Bystander CPR
DEFINITIONS	Cardiac Arrest: End of cardiac mechanical activity determined by the absence of signs of circulation. Cause of Arrest: Presumed cardiac unless evidence suggested external causes (trauma, hanging, drowning, drug overdose, asphyxia), respiratory diseases, cerebrovascular diseases, malignant tumors, or any other non-cardiac cause. Japanese CPR Guidelines: Based on the AHA and the International Liaison Committee on Resuscitation (ILCOR) 2000 guidelines
OUTCOME	Primary Outcome: Favorable neurological outcome 1 month after cardiac arrest, defined as Glasgow-Pittsburgh cerebral performance category 1 (good performance) or 2 (moderate disability). Secondary Outcomes: Return of spontaneous circulation (ROSC) before hospital arrival and 1-month survival.
DESIGN	Observational: Prospective cohort study

HOW SERIOUS WAS THE RISK OF BIAS?

ASIDE FROM THE EXPOSURE OF INTEREST DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or did statistical adjustments address the imbalance).	Table 3 shows the demographic characteristics and other prognostic data for the different groups. There were some statistically significant differences between CPR and non-CPR group, and the compression only vs conventional CPR groups, but these differences are probably not clinically relevant: <u>Non-Cardiac Arrest</u> Time from EMS getting called to EMS performing CPR Compression only group: 8.5 minutes Conventional CPR group: 9 minutes <u>Cardiac Arrest</u> Time from EMS getting called to EMS delivering a shock Compression only group: 8.5 minutes: 11.8 minutes Conventional CPR group: 9 minutes: 9.2 minutes <u>Bystander CPR versus no CPR</u> Younger (4.9 vs 5.3 years) Less likely to have had a witnessed arrest (75% vs 70%) More likely to have ventricular fibrillation (6% vs 4%). A regression analysis was used to account for differences in potential confounders.
Were the circumstances and methods for detecting the outcome similar?	Some of the outcome variables were objective and obtained from the chart. The authors determined cause of cardiac arrest. It is not clear who assigned the primary outcome at 1 month, but the Glasgow Pittsburgh scale is a relatively objective measure.
Was follow-up sufficiently complete?	<1% of patients did not have outcome data available for primary outcome.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

N = 5,170
29% cardiac, 71% non-cardiac
1 month survival: 9.2%
1 month favorable neurologic survival: 3.2%
47% with bystander CPR (30% conventional, 17% compression only)

HOW PRECISE IS THE ESTIMATE OF THE RISK?

See confidence intervals in the clinical bottom line. The large sample size resulted in narrow (precise) confidence intervals for most adjusted odds ratios.

REGRESSION: FAVORABLE NEUROLOGIC OUTCOMES AT 1 MONTH

NUMERATOR	DENOMINATOR	ADJUSTED OR (95%CI)
Any bystander CPR (4.5%)	No Bystander CPR (1.9%)	2.59 (1.81, 3.71)
Age 1-17 years (4.1%)	Age 0-1 years (1.7%),	1.60 (1.07, 2.36)
Ventricular fibrillation (20.6%)	Not ventricular fibrillation (2.3%)	6.21 (3.93, 9.80)
Witnessed by others (10.3%)	No witness (1.3%)	6.43 (4.08, 10.1)
Witnessed by family (6.7%)	No witness (1.3%)	5.21 (3.44, 7.90)
Earlier initiation of CPR by EMS (for each 1 minute increase)		0.91 (0.86, 0.97)

NON-CARDIAC ARREST: FAVORABLE NEUROLOGIC OUTCOME AT 1 MONTH

GREEN = Statistically Significant RED = Not Statistically Significant	Proportion	Absolute Risk Difference (95% CI)	Relative Risk (95% CI)
Any Bystander CPR	64/1,654 (3.9%)	2.2% (1.1, 3.3%)	0.44 (0.29, 0.66)
No Bystander CPR	34/2,010 (1.7%)		
Conventional CPR	56/1,055 (5.3%)	4.0% (2.2, 5.6%)	0.25 (0.12, 0.54)
Chest compression only CPR	8/597 (1.3%)		

CARDIAC ARREST: FAVORABLE NEUROLOGIC OUTCOME AT 1 MONTH

GREEN = Statistically Significant RED = Not Statistically Significant	Proportion	Absolute Risk Difference (95% CI)	Relative Risk (95% CI)
Any Bystander CPR	46/785 (5.9%)	3.8% (1.9%, 5.8%)	0.36 (0.21, 0.60)
No Bystander CPR	19/709 (2.7%)		
Conventional CPR	31/496 (6.3%)	0.9% (-2.9, 4.1%)	0.86 (0.47, 1.56)
Chest compression only CPR	15/279 (5.4%)		

SUMMARY

NON-CARDIAC ARREST	Any CPR > No CPR Conventional CPR > Compression only CPR
CARDIAC ARREST	Any CPR > No CPR Conventional CPR = Compression only CPR

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	These patients and bystanders were Japanese. In Japan, it is estimated that roughly 10% of the adult population is trained in conventional CPR. Cause of arrest was similar to U.S. statistics, but many factors are either unknown or dissimilar to USA demographics.
Was follow-up sufficiently long?	Yes. The primary outcome was measured at 1 month. That appears to be sufficient to determine long term neurologic status in the majority of patients.
Is the exposure similar to what might occur in my patient?	Unclear. The rate of bystander CPR varies by location. In NYC where people live and work in close proximity the potential of early CPR by bystanders is increased. The rate of CPR training likely doesn't reach the 10% in this study.
What is the magnitude of the risk?	In this study, conventional CPR lead to improved neurological function at one month after arrest from a non-cardiac cause when compared to compression only CPR. On the other hand, any CPR is better than no CPR, and a program of compression only CPR is theoretically easier to teach and disseminate to the population. In this study, only 47% of out-of-hospital arrests had any CPR. If that number can be improved upon it may lead to improved outcomes.
Are there any benefits that offset the risks associated with exposure?	One of the exposures in this study is bystander CPR. There appears to be a substantial benefit without accompanying risk. There could potentially be a risk associated with chest compressions and rescue breathing if the interventions are not indicated.

CLINICAL BOTTOM LINE

BACKGROUND: Previous studies in adult cardiac arrest have demonstrated that outcomes are equivalent when compression only CPR is compared to standard CPR (compressions and ventilation). Unlike adults, in pediatrics the primary cause of a cardiopulmonary arrest is typically respiratory in origin.

CLINICAL QUESTION: In out-of-hospital pediatric cardiac arrest in which bystanders initiate CPR does compression only CPR when compared to standard CPR (chest compressions and rescue breathing) result in improved neurologic outcomes at 1 month?

DESIGN/VALIDITY: The was a well-design prospective cohort study which included 5,170 pediatric patients with an out-of-hospital cardiac arrest with 29% of cardiac etiology and 71% of non-cardiac cause. 47% had bystander CPR (30% conventional CPR, 17% compression only CPR).

PRIMARY RESULTS: Overall, favorable neurologic survival at 1 months was 3.2%. Patients with both cardiac and non-cardiac arrests had a higher proportion of favorable neurologic outcome if bystander CPR was performed. Non-cardiac arrest (Any bystander CPR – No bystander CPR) = 2.2% (1.1, 3.3%), Cardiac arrest (Any bystander CPR – No bystander CPR) = 3.8% (1.9%, 5.8%). Patients with non-cardiac arrests had a higher proportion of favorable neurologic outcome when conventional CPR was performed by a bystander then when compression only CPR was performed. Non-cardiac arrest (Conventional CPR – Compression Only CPR) = 4.0% (2.2, 5.6%). In cardiac arrest, there was no difference in favorable neurologic outcome between conventional CPR and Compression only CPR. Cardiac arrest (Conventional CPR – Compression Only CPR) = 0.9% (-2.9, 4.1%).

REGRESSION: FAVORABLE NEUROLOGIC OUTCOMES AT 1 MONTH		
NUMERATOR	DENOMINATOR	ADJUSTED OR (95%CI)
Any bystander CPR (4.5%)	No Bystander CPR (1.9%)	2.59 (1.81, 3.71)
Age 1-17 years (4.1%)	Age 0-1 years (1.7%),	1.60 (1.07, 2.36)
Ventricular fibrillation (20.6%)	Not ventricular fibrillation (2.3%)	6.21 (3.93, 9.80)
Witnessed by others (10.3%)	No witness (1.3%)	6.43 (4.08, 10.1)
Witnessed by family (6.7%)	No witness (1.3%)	5.21 (3.44, 7.90)
Earlier initiation of CPR by EMS (for each 1 minute increase)		0.91 (0.86, 0.97)

NON-CARDIAC ARREST: FAVORABLE NEUROLOGIC OUTCOME AT 1 MONTH			
GREEN = Statistically Significant RED = Not Statistically Significant	Proportion	Absolute Risk Difference (95% CI)	Relative Risk (95% CI)
Any Bystander CPR	64/1,654 (3.9%)	2.2% (1.1, 3.3%)	0.44 (0.29, 0.66)
No Bystander CPR	34/2,010 (1.7%)		
Conventional CPR	56/1,055 (5.3%)	4.0% (2.2, 5.6%)	0.25 (0.12, 0.54)
Chest compression only CPR	8/597 (1.3%)		

APPLICABILITY: The large sample size likely makes this study generalizable to most pediatric populations though there may be differences in the Japanese health care system that would limit its applicability to U.S. populations.

AUTHOR'S CONCLUSION: "For children who have out-of-hospital cardiac arrests from non-cardiac causes, conventional CPR (with rescue breathing) by bystander is the preferable approach to resuscitation. For arrests of cardiac causes, either conventional or compression-only CPR is similarly effective."

SUMMARY	
NON-CARDIAC ARREST	Any CPR > No CPR Conventional CPR > Compression only CPR
CARDIAC ARREST	Any CPR > No CPR Conventional CPR = Compression only CPR

POTENTIAL IMPACT: This study provides data to support that the use of conventional CPR may lead to earlier return to spontaneous circulation and improved neurological outcomes at one month when compared to compression only CPR. In pediatric arrest of cardiac etiology compression only CPR was equivalent to standard CPR. The study also emphasizes the importance of any CPR over no CPR use, and raises the point that investing in CPR training of either method can improve outcomes.

2015 American Heart Association guidelines for CPR emphasize a resuscitation sequence of Circulation Airway-Breathing (CAB) over the previously taught Airway Breathing-Circulation (ABC). Acknowledging that the optimal sequence of CPR has not been determined so that starting with Compressions would only minimally delay the onset of ventilations for approximately 20 seconds. Asphyxial arrest more common in pediatrics and both compressions and ventilations required. Compression only CPR may be considered for rescuers unwilling or unable to perform rescue breaths in a patient with cardiac arrest.

BASIC LIFE SUPPORT:
PEDIATRIC OUT-OF-HOSPITAL BYSTANDER CPR

In pediatric out-of-hospital cardiac arrest (OHCA) does bystander CPR (conventional CPR or compression only CPR) when compared to no bystander CPR result in improved survival to hospital discharge and neurologically favorable survival at hospital discharge?

Nicole Gerber M.D., Dennis Heon M.D.
October 2014

Naim MY, Burke RV, McNally BF, Song L, Griffis HM, Berg RA, Vellano K, Markenson D, Bradley RN, Rossano JW.

ASSOCIATION OF BYSTANDER CARDIOPULMONARY RESUSCITATION WITH OVERALL AND NEUROLOGICALLY FAVORABLE SURVIVAL AFTER PEDIATRIC OUT-OF-HOSPITAL CARDIAC ARREST IN THE UNITED STATES:
A REPORT FROM THE CARDIAC ARREST REGISTRY TO ENHANCE SURVIVAL SURVEILLANCE REGISTRY.

JAMA Pediatr. 2017 Feb 1;171(2):133-141.
PubMed ID: 27837587

STUDY DEFINITIONS	
POPULATION	Inclusion: <18 years, non-traumatic, out of hospital arrest defined as apnea or unresponsiveness with attempted CPR or defibrillation Exclusion: 1. Traumatic arrest 2. Obvious signs of death (rigor mortis or dependent lividity) 3. Do not resuscitate order 4. Arrests in medical facilities or nursing homes 5. Arrests witnessed by 911 responders Setting: Cardiac Arrest Registry to Enhance Survival (CARES) database. Registry Data from call centers, responding EMS personnel, receiving hospitals. Includes patients in 37 states, 1/2013-12/2015
EXPOSURE	Bystander CPR: CPR by a layperson or layperson with medical training not part of the organized emergency medical response. Any Bystander CPR: Conventional or Compression Only Bystander CPR Conventional Bystander CPR: Chest compressions and rescue breaths Compression Only Bystander CPR: Chest compression without rescue breaths
NO EXPOSURE	No Bystander CPR
OUTCOME	Primary Outcomes: 1. Survival to hospital discharge 2. Neurologically favorable survival at discharge defined as a Cerebral Performance Category Score of 1 (no neurologic disability) or 2 (moderate disability). See Appendix
DESIGN	Retrospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	Yes. (Table 1). Those who did and did not receive bystander CPR were similar with regards to most prognostic factors. The authors highlight that an observational design does not allow for the influence of unmeasured confounders. Because this is a large registry they were not able to determine the underlying cause of the arrest which is also a large factor associated with outcome. However, given that this is such a large database, they likely had similar numbers of all etiologies in both groups. There was a large difference in race. Bystander CPR was performed in 56.3% of whites, 39.4% of African Americans and 43.3% of Hispanic patients. It also would have been interesting to see a breakdown of age in the 1-18 year old group to see if there were any differences between school aged children and teenagers.
Were the circumstances and methods for detecting the outcome similar?	Yes. All of the data used for their analysis comes from the CARES database. Data comes from 911 call centers, responding EMS professionals and receiving hospitals. For the Cerebral performance category information, there is a contact person at each participating hospital who is trained on definitions and data entry. They do not specifically say if the training is standardized.
Was follow-up sufficiently complete?	In the discussion, the authors indicate that 72 patients (1.8%) had missing data and were excluded from analysis, suggesting that they had information up to the time of hospital discharge on all remaining survivors.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

Demographic Data
N = 3,900
< 1 year: 59.4%
Location of Arrest: Home/Residence: 83.7%
Unwitnessed: 72.2%
Non-shockable rhythm (Asystole, PEA): 92.2%
Survival: 11.3%
Survival (neurologically intact): 9.1%
Bystander CPR: 46.5% (1,814/3,900)
- Family member: 67.4%
- Layperson: 22.9%
- Layperson with medical training: 9.1%

Bystander CPR: White 56.3%, African American 39.4%, Hispanic 43.3%.

Primary Analysis: Any Bystander CPR vs No Bystander CPR

ANY BYSTANDER CPR (YES) VS NO BYSTANDER CPR (NO)				
	YES	NO	Difference	Adjusted Odds Ratio
Survival to Hospital Discharge	13.19%	9.48%	3.71%	1.57 (1.25, 1.96)
Neurologically Favorable outcome	10.32%	7.59%	2.73%	1.54 (1.21, 1.98)

Other Independent Predictors:
Survival to hospital discharge: Age > 1 year, female, witnessed, non-home, shockable
Neurologically favorable discharge: Age > 1 year, white race, witnessed, non-home, shockable

Secondary Analysis: Type of Bystander CPR vs No Bystander CPR
N = 1,411/1,814 (77.8%) with bystander CPR type available
Conventional CPR: 49.4%
Compression Only CPR: 50.6%

COMPRESSION ONLY BYSTANDER CPR (YES) VS NO BYSTANDER CPR				
	YES	NO	Difference	Adjusted Odds Ratio
Survival to Hospital Discharge	12.09%	9.37%	3.53%	1.40 (1.05, 1.87)
Neurologically Favorable Outcome	9.59%	7.54%	2.05%	1.37 (0.99, 1.89)

CONVENTIONAL BYSTANDER CPR (YES) VS NO BYSTANDER CPR (NO)				
	YES	NO	Difference	Adjusted Odds Ratio
Survival to Hospital Discharge	16.79%	9.37%	7.42%	2.23 (1.69, 2.95)
Neurologically Favorable Outcome	12.89%	7.54%	5.35%	2.06 (1.51, 2.79)

CONVENTIONAL VS COMPRESSION ONLY BYSTANDER CPR			
	Conventional	Compression Only	Difference
Survival to Hospital Discharge	16.79%	12.09%	4.7%
Neurologically Favorable Outcome	12.89%	9.59%	3.3%

Proportion in the tables represent the adjusted risk or adjusted risk difference.
The authors did not specify a value for a clinically significant risk difference.

Subgroup Analysis: Outcomes by Age

SUBGROUP ANALYSIS: OUTCOMES BY AGE		
	INFANTS (< 1ye	CHILDREN
Any bystander CPR vs No bystander CPR	No Difference	Improved
Conventional CPR vs No bystander CPR	Improved	Improved
Compression only CPR vs No bystander CPR	No Difference	Improved

HOW PRECISE IS THE ESTIMATE OF THE RISK?
For all of the outcomes, given how large the database is, the confidence intervals are narrow.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Yes. The CARES database has a catchment area of over 90 million people in 37 states across the united states. Although the state of NY does not as a whole participate in the database, several cities in and surrounding NY do participate so the patients are likely to be similar to our patients. However, this study population had higher rates of bystander CPR and survival the previous studies.
Was follow-up sufficiently long?	One of the limitations of this study is that there is no long term follow up of the survivors, this is only survival to hospital discharge and neurological outcome at discharge. However, this is still an accepted marker for successful resuscitation. In addition, it would have been helpful to see the proportion of patients in each of the categories of the primary outcome and not just the proportion in categories 1 and 2 combined.
Is the exposure similar to what might occur in my patient?	Yes. Our patients are probably subject to similarly low rates of Bystander CPR and Compression only CPR over conventional CPR.
What is the magnitude of the risk?	Bystander CPR resulted in a modest improvement in survival to hospital discharge compared to No Bystander CPR (13.19% - 9.58% = 3.71%) and neurological favorable survival to hospital discharge (Adjusted Risk Difference: 10.32% - 7.59% = 2.73%).
Are there any benefits that offset the risks associated with exposure?	There are unlikely to be any benefits to not receiving bystander CPR. It was of been helpful to see the proportion in each group with neurologic survival scores 3 (severe disability, dependent in activities of daily living), stage 4 (persistent vegetative state) and stage 5 (dead).

CLINICAL BOTTOM LINE

BACKGROUND: The adult literature has demonstrated that bystander CPR leads to improved survival, but the benefit of bystander CPR is less clear for pediatric patients who have a higher proportion of respiratory arrest and a lower proportion of shockable rhythms. The 2015 American Heart Association guidelines recommend compression only CPR in adults. Evidence in children in cardiac arrest indicates that compression only CPR is equivalent to standard CPR with both compressions and ventilation. Evidence in children with asphyxial arrest (the most common cause) indicates that outcomes are better with standard CPR than with compression only CPR. It is thought that a lay provider may be more willing to provide chest compressions without ventilation.

CLINICAL QUESTION: In pediatric out-of-hospital cardiac arrest (OHCA) does bystander CPR (conventional CPR or compression only CPR) compared to no bystander CPR result in improved survival to hospital discharge and neurologically favorable survival at hospital discharge?

DESIGN/RISK OF BIAS: This was a well-designed, retrospective, cohort study from an emergency medical services database that included 3,900 patients less than 18 years of age with out-of-hospital cardiac arrest. The CARES database has a catchment area of over 90 million people in 37 states across the United States and obtains data from 911 call centers, responding EMS professionals and receiving hospitals. There were minimal validity concerns given the size of the cohort and the standardized methods used to obtain information for the CARES database. However, the authors acknowledge that it was not possible to clearly identify the etiology of the arrest and that type of bystander CPR performed was only available in 78% of the patients.

The primary outcomes were survival to hospital discharge and neurologically favorable survival at discharge defined as a Cerebral Performance Category Score of 1 (no neurologic disability) or 2 (moderate disability). The multivariate analysis compared any bystander CPR and each type of bystander CPR (conventional and compression only CPR) for both of the outcomes to patients without bystander CPR. A subgroup analysis comparing infant to older children was presented. It may have been helpful to directly compare the outcomes of conventional and compression only CPR to each other. In addition, it would have been helpful to present the proportion of patients in each of the categories of the primary outcome and not just the proportion in categories 1 and 2.

PRIMARY RESULTS: Bystander CPR was performed in 46.5% of arrests (Conventional CPR: 49.4%, Compression Only CPR: 50.6%). Bystander CPR resulted in improved odds of survival to hospital discharge (AOR: 1.57, 95% CI (1.25, 1.96)) as well as neurologically favorable survival (AOR 1.54, 95% CI (1.21, 1.98)). In a sub-analysis of the 1,411 (78%) children where data was available on the type of Bystander CPR performed, both Conventional CPR ((AOR: 2.23, 95% CI (1.69, 2.95) and Compression Only CPR (AOR: 1.14, 95% CI (1.05, 1.97) were associated with increased survival to hospital discharge. Only Conventional CPR (AOR: 2.06, 95% CI (1.51, 2.79) was associated with neurologically favorable survival. In children over 1 year of age any bystander CPR, and both standard and compression only CPR resulted in improved outcome. In infants, only conventional CPR resulted in improved outcomes.

APPLICABILITY: Although the CARES database does not specifically include New York City, given the large catchment size covering multiple areas of the United States, this information is relevant to our population of pediatric patients who undergo OHCA. However, the population in the study had a higher rate of bystander CPR and higher rates of survival to hospital discharge and neurologically intact survival then previously reported.

AUTHOR'S CONCLUSION: "Bystander CPR is associated with improved outcomes in children with Out-of-hospital cardiac arrest. Conventional Bystander CPR is associated with improved outcomes compared with Compression only CPR, and among infants, there was no benefit of Bystander CPR unless ventilations were provided. Efforts to improve the provision of CPR in minority communities and increasing the use of conventional Bystander CPR may improve outcomes for children with Out-of-hospital cardiac arrest."

POTENTIAL IMPACT: This study is currently the best evidence available supporting the importance of Bystander CPR in pediatric Out-of-Hospital Cardiac Arrest. This study also highlights that although efforts need to be made to standardize CPR training, and Compression only CPR has been shown to be effective in the adult population, for pediatric patients, especially those less than 1 year of age, it is important to continue to perform conventional CPR that includes rescue breathing.

84% of arrests occurred in the home and 67% of the time that bystander CPR was performed it was performed by a family member. This highlights opportunities to recommend CPR training for caregivers. In addition, it may be helpful to increase the use of dispatcher assisted CPR targeted to the pediatric population and leverage technologic solutions such a phone application to provide CPR guidance. Finally, these efforts to increase bystander CPR may have the greatest impact in non-white communities.

APPENDIX: CEREBRAL PERFORMANCE CATEGORY SCALE

CEREBRAL PERFORMANCE CATEGORY SCALE	
1	Full recovery or mild disability
2	Moderate disability but independent activities of daily living
3	Severe disability, dependent in activities of daily living
4	Persistent vegetative state
5	Dead

BASIC LIFE SUPPORT: PULSE PALPATION

In pediatric patients, whose circulation is supported by extracorporeal circulatory life support due to circulatory arrest or failure, what are the test characteristics of pulse palpation within 10 seconds by physicians and nurses not directly involved in the patient's care?

Marc Auerbach, M.D., Dennis Heon, M.D.
January 2009

Tibballs J, Russell P.

RELIABILITY OF PULSE PALPATION BY HEALTHCARE PERSONNEL TO DIAGNOSE PEDIATRIC CARDIAC ARREST.

Resuscitation. 2009 Jan;80(1):61-4.
PubMed ID: 18992985

STUDY DEFINITIONS	
POPULATION	Inclusion: Patients on extracorporeal circulatory life support (ECLS) by veno-arterial extracorporeal membrane oxygenation (ECMO) or left ventricular assistance device (LVAD) for circulatory arrest or failure. Blood flow is non-pulsatile until the patient's heart resumes spontaneous ejection and generate a pulse. Exclusion: Patients in which the investigator nurse or physician with access to all patient circulatory data did not agree on the presence of a pulse Setting: Single Children's Hospital PICU (Australia), 4/2007-1/2008
TEST	Pulse palpation in an infant or child by doctors and nurses entering the intensive care unit for other reasons or recruited from the emergency department. Informed that non-pulsatile blood circulation for the patient was provided by a machine but a spontaneous pulsatile component to blood flow may or may not be present. Instructed to palpate any pulse of their choice excluding the cardiac apex and decide on "pulse present" or "pulse absent" within 10 seconds
REFERENCE STANDARD	Presence or absence of a true pulse at possible locations (radial, ulnar, brachial, axillary, carotid, femoral, popliteal, dorsalis pedis, and posterior tibial) determined by the investigators and the bedside nurse using unhurried palpation and observation of invasively monitored blood pressure and pulse pressure (if any).
OUTCOME	Test characteristics
DESIGN	Observational: Prospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. Patient on extracorporeal membrane oxygenation (ECMO) or who had a left ventricular assist device (LVAD) served as surrogates for cardiac arrest patients.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The presence or absence of a pulse was determined by the investigator and bedside nurse using all clinical and monitoring information available. If they did not agree on presence or absence of a pulse then patient was excluded.
Were those interpreting the test and reference standard blind to the other results?	Yes. Those assessing the pulse were blinded to the data that was used as a reference standard. The monitor was obscured, arterial line was not visible, and the anterior chest of patient was covered. Those determining the reference standard used a variety of data points to determine the presence or absence of a pulse including pulse palpation.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	The reference standard was a composite outcome. The presence or absence of a pulse was determined by the investigator and bedside nurse using all clinical and monitoring information available.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 209 Palpations:
ECMO: 161, LVAD: 48
N = 16 patients, 75% < 1 year
N = 209 Healthcare personnel: RN 101, MD 108
Non-acute care disciplines: RN 66%, MD 48%
Location of Palpation:
RN: Brachial 65%, Femoral 30%
MD: Brachial 55%, Femoral 37%
90% of palpation in vessels proximal to or larger than reference standard location
Within 10 seconds: 86%

		PULSE REFERENCE		
		ABSENT	PRESENT	
PULSE PALPATION	ABSENT	110	29	139
	PRESENT	18	52	70
		128	81	209

Positive Test = Pulse Absent (Not palpated)
Negative Test = Pulse Presence (Palpated)

Prevalence (without pulse): 128/209 = 61.2%
Mean Pulse Pressure (without pulse): 6 +/- 5 mmHg
Mean Pulse Pressure (with pulse): 23 +/- 6 mmHg

Primary Outcomes: Test Characteristics
Test characteristics are for the absence of a pulse
Sensitivity: 110/128 = 85.9%, 95% CI (78.9, 90.9%)
Specificity: 52/81 = 64.2%, 95% CI (53.3, 73.8%)
Predictive Value of a Positive Test: 110/139 = 79.1%, 95% CI (71.6, 85.1%)
Predictive Value of a Negative Test: 52/70 = 74.3%, 95% CI (63, 83.1%)
Likelihood ratio of a Positive Test: (110/128)/(29/81) = 2.4, 95% CI (1.8, 3.2)
Likelihood ratio of a Negative Test: (18/128)/(52/81) = 0.22, 95% CI (0.14, 0.35)
Accuracy: (110 + 52)/209 = 78%

Secondary Outcomes:
Subgroup Analysis: See Appendix

PULSE PRESSURE	SENSITIVITY
0	89%
≤ 10	87%
≥ 10, ≤ 15	87%

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Unclear. In this study, the pulse check is the test. There may be great variable in expertise and experience in determining pulse presence. Patient characteristics such as body mass index or edema may influence palpation. It may have been helpful to look at the accuracy of pulse palpation based on specific sites on a single patient.
Are the study results applicable to the patients in my practice?	Yes. Although these patients were in the ICU on extracorporeal circulation this is a reasonable model to use to evaluate the ability to do pulse checks in children.
Will the test results change my management strategy?	Yes, I will have less faith in the ability of health care providers to accurately detect the presence or absence of a pulse.
Will patients be better off as a result of the test?	Yes. Pulse palpation is a crucial decision node in the care of critically ill patient. This study found it to be unreliable. Current resuscitation guidelines reflect this unreliability. Alternative methods such as point of care ultrasound should be investigated.

CLINICAL BOTTOM LINE

BACKGROUND: Pulse palpation is a critical decision node during resuscitations. The presence of absence of a pulse dictates therapeutic options. Errors in pulse palpation can lead to withholding resuscitative efforts (e.g. chest compressions) in a patient without a pulse in which a pulse is thought to be present. In addition, patients may receive unnecessary harmful interventions (e.g. cardioversion) if a pulse is present and it is thought to be absent. Prior studies have supported visualizing or auscultation as being more accurate than pulse checks. There is also mixed data on the “best” site for palpation (femoral, apical, carotid, brachial).

CLINICAL QUESTION: In pediatric patients, whose circulation is supported by extracorporeal circulatory life support due to circulatory arrest or failure, what are the test characteristics of pulse palpation within 10 seconds by physicians and nurses not directly involved in the patient’s care?

DESIGN/RISK OF BIAS: This was a well-designed, prospective cohort study using a novel criterion standard for pulse presence or absence. The 16 patients (75% < 1 year of age) were those on extracorporeal circulatory life support (ECLS) for circulatory arrest or failure. ECLS was delivered by veno-arterial extracorporeal membrane oxygenation (ECMO: 161 palpations) or left ventricular assistance device (LVAD: 48 palpations). Blood flow in these patients is non-pulsatile until the patient’s heart recovers to resume spontaneous ejection and generate a pulse. Rescuers were recruited from nurses and physicians not directly involved in the patient’s ICU care and blinded to the patient’s chest and monitor data. The rescuers were asked to limit the palpation time to less than 10 seconds. Those determining the reference standard used a variety of data points to determine the presence or absence of a pulse including pulse palpation.

PRIMARY RESULTS: Pulse palpation was neither sensitive (85.9%, 95% CI (78.9, 90.9%) nor specificity (64.2%, 95% CI (53.3, 73.8%)). Essentially pulse palpation stratified a group of patients in which a pulse was absent 61% of the time into a group with an absent pulse 79% of the time if a pulse was not palpated and a group with an absent pulse 26% of the time if a pulse was palpated. The likelihood ratios in this study were weak (2.4 for a positive test and 0.22 for a negative test).

SUBGROUP (N = # PALPATIONS)	SENSITIVITY (95% CI)	SPECIFICITY (95% CI)
All rescuers (209)	86% (79, 91%)	64% (53, 74%)
Infants (191)	85% (77, 91%)	67% (55, 77%)
Children (18)	100% (66, 100%)	44% (14, 79%)
All doctors (108)	88% (78, 94%)	67% (51, 79%)
All nurses (101)	84% (73, 91%)	62% (46, 75%)
Acute care doctors (56)	94% (81, 98%)	67% (45, 83%)
Acute care nurses (61)	85% (71, 93%)	62% (41, 79%)
Non-acute care doctors (52)	81% (64, 91%)	67% (45, 83%)
Non-acute care nurses (40)	82% (61, 93%)	61% (39, 80%)
Brachial palpation (125)	86% (76, 92%)	67% (53, 78%)
Femoral palpation (70)	85% (72, 92%)	56% (33, 76%)

APPLICABILITY: 91% of palpations occurred in patients < 1 year of age with a mean age of 4 weeks. It is unclear if study's results could be generalizable to older children who generally have a higher pulse pressure and therefore should a more identifiable pulse.

AUTHOR'S CONCLUSION: "Pulse palpation is unreliable to diagnose paediatric cardiac arrest. Rescuers misdiagnose on 22% of occasions and which may lead them to withhold external cardiac compression on 14% of occasions when needed and on 36% to give it when not needed. Brachial palpation is slightly more reliable than femoral palpation."

POTENTIAL IMPACT: This study highlights the unreliability of pulse palpation by health care providers. Pulse palpation is a crucial decision node in patients in a patient in critical condition. American Heart Association Pediatric Advanced Life Support 2015 Guidelines (PubMed ID: 26472999) recommend excluding a pulse check for lay person cardiopulmonary resuscitation and to limit the pulse check to 10 seconds for health care providers. "If, within 10 seconds, you don't feel a pulse or are not sure if you feel a pulse, begin chest compressions" Recommended locations for a pulse check are: infant: brachial, child: femoral or carotid and adult: carotid. Alternative methods for assessing a pulse, such as point of care ultrasound, should be investigated.

POST RESUSCITATION CARE: THERAPEUTIC HYPOTHERMIA

In pediatric patients who remain comatose and require mechanical ventilation after return of spontaneous circulation from an out-of-hospital cardiac arrest does therapeutic hypothermia (target temperature: 33 C for 48 hours) when compared to therapeutic normothermia (target temperature: 36.8 C) improve the rate of survival with a good neurobehavioral outcome at 12 months?

Shweta Iyer M.D., Joshua Beiner M.D.
February 2017

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THERAPEUTIC HYPOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST IN CHILDREN.

N Engl J Med. 2015 May 14;372(20):1898-908.
PubMed ID: 25913022

STUDY DEFINITIONS	
POPULATION	Inclusion: > 48 hours to < 18 years, out-of-hospital cardiac arrest requiring chest compressions for ≥ 2 minutes, comatose and dependent on mechanical ventilation after return of spontaneous circulation (ROSC) Exclusion: Inability to randomize within 6 hours after ROSC, Glasgow Coma Scale motor subscale score of 5 or 6, decision to withhold aggressive treatment, major trauma associated with the cardiac arrest, VABS-II score < 70 before cardiac arrest (baseline) Setting: 38 Children's Hospital Pediatric ICUs (U.S., Canada), 9/2009-12/2012
INTERVENTION	Therapeutic Hypothermia: Target temperature, 33.0°C (32-34 C) for 48 hours then rewarmed over 16 hours to target temperature of 36.8 (36-37.5) and then maintained at 36.8 for 56 hours for a total time of 120 hours.
CONTROL	Therapeutic Normothermia: Target temperature, 36.8°C (36-37.5) for 120 hours
CO-INTERVENTIONS	All patients pharmacologically paralyzed and sedated Blanketrol III temperature management unit (blankets anteriorly and posteriorly)
OUTCOME	Primary Outcome: Proportion of survivors with a Vineyard Adaptive Behavior Scale, 2nd Edition (VABS-II) score ≥ 70 at 12 months (See Appendix) Secondary Outcomes: 1. Change in VABS-II score from baseline to 12 months 2. Mortality at 12 months 3. Global cognition score 4. Safety: Blood product use, infection, serious arrhythmia within 7 days, 28 day mortality
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Randomization was performed using permuted blocks and stratified by study center and age (< 2 years, 2-11 years, ≥ 12 years).
Was randomization concealed?	Yes. Patients were allocated in a 1:1 ratio to therapeutic hypothermia or therapeutic normothermia. While not explicitly stated, it does not appear that there was an opportunity to bias the allocation process.
Were patients in the study groups similar with respect to known prognostic factors?	Yes and No. Most patient characteristics (i.e. age, cause of cardiac arrest) were similar in the two study groups. There was minor difference in some factors that could possible bias the study results in favor of therapeutic hypothermia. In the normothermia group, there was a higher number of pre-existing conditions (111 vs 96), a lower rate of bystander CPR (63% vs 68%), a lower proportion with an initial shockable rhythm (6% vs 9%) and a higher proportion requiring chest compression at hospital arrival (73% vs 64%). A regression analysis was not performed to account for these differences.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Caregivers and research staff in the ICU could be aware of the treatment assignments of the patients, although the primary outcome assessments were blinded. VABS-II data was collected centrally, through phone interviews and parental report. It is unclear if knowledge of the treatment assignment would bias later scoring of the VABS-II.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. See CONSORT diagram. In the modified intention to treat population 97% (138/142) of the hypothermia group and 95% (122/128) of the normothermia group were included in the analysis of the primary outcome.
Were patients analyzed in the groups to which they were randomized?	This trial was a modified intention-to-treat analysis for the primary outcome, excluding children with poor neurobehavioral function (i.e. VABS-II score <70) before cardiac arrest. Initially there were 155 people assigned in the hypothermia group but only 142 people were eligible due to these restrictions. Similarly, there were 140 people in the normothermia group but only 128 people were eligible for primary analysis. Within the normothermia group, 1 patient ended up receiving hypothermia therapy but was still allocated to the normothermia group. A per protocol analysis of the modified intention to treat population was conducted (see article supplement) which removed patients not receiving the assigned treatment, patients randomized over 6-hours after return of spontaneous circulation, and/or patients otherwise technically not meeting criteria. The results did not markedly affect the significance of the study findings or estimated treatment effects.
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N =138 (hypothermia), 122 (normothermia)
Median age: 2 years
Respiratory cause of arrest: 72%
No Preexisting medical condition: 52%
Witnessed arrest: 39%
Bystander CPR: 66%

PRIMARY OUTCOME:

NEUROBEHAVIORAL OUTCOME AT 12 MONTH

	ALIVE AND VABS-II ≥ 70	NOT ALIVE OR ALIVE WITH A VABS-II < 70	
HYPOTHERMIA	27	111	138
NORMOTHERMIA	15	107	122
	42	218	260

Prevalence (Alive with VABS > 70): 42/260 = 16.2%
Risk Hypothermia: 27/138 = 19.6%
Risk Normothermia: 15/122 = 12.3%
Risk Difference: 19.6%–12.3%= 7.3%, 95%CI (-1.5, 16.1%)
Relative Risk: 19.6%/12.3% = 1.54, 95% CI (0.86, 2.76)

SECONDARY OUTCOMES:

Mortality at 1 year:
Hypothermia: 38%
Normothermia: 29%
Risk Difference: 9.1%, 95% CI (-1.8, 19.9%)

Change in VABS-II score (baseline -12 months): p=0.13

Survival Over Time:
Hypothermia: 149±14 days
Normothermia: 119±14 days p=0.04

Safety (Table3): No difference: Infection, bleeding and serious arrhythmias within 7 days

Mortality at 28 days:
Hypothermia: 57%
Normothermia: 67%
Risk Difference: 10%, 95% CI (-1.1, 20.8%)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The confidence intervals are relatively wide. The 95% confidence interval for the absolute risk difference of 7.3% (-1.5 to 16.1%) includes 0 so the difference is not statistically significant. The authors specified a clinical significant difference of 20% in their sample size determination.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. Pediatric patients with out of hospital cardiac arrest who have return of spontaneous circulation are rare. It took 38 Children's hospital to enroll approximately 200 patients over 40 months (4 patients/center/year). When we do see these patients, they are similar to the patients in the study (i.e. demographics, past medical history - often preexisting lung or airway disease, and cause of cardiac arrest as usually respiratory). Additionally, approximately 50% of the children in both groups had no pre-existing medical condition and were healthy before, which is similar to our Bellevue PES population and the patients with numerous pre-existing conditions are similar to our NYU patients.
Were all patient important outcomes considered?	Yes. The outcomes considered included proportion of patients with VABS II scores $\geq$70 after 12 months, change in VABS II score from baseline to 12 months, survival at 1 year, and survival over time. It may have been helpful to perform a subgroup analysis on those with and without a pre-existing condition.
Are the likely treatment benefits worth the potential harm and costs?	Given that the treatment overall has no statistically significant benefit, currently the potential treatment benefit of longer survival time is not worth the potential harm (i.e. side effects of hypothermia treatment) and costs/resources.

CLINICAL BOTTOM LINE

BACKGROUND: Initial studies demonstrated that therapeutic hypothermia was effective in comatose adults with return of spontaneous circulation after out-of-hospital cardiac arrest primarily due to shockable rhythms. More recent studies utilizing therapeutic normothermia (i.e. avoiding fever) have questioned the benefit of therapeutic hypothermia. Data about this intervention in children is limited.

CLINICAL QUESTION: In pediatric patients who remain comatose and require mechanical ventilation after return of spontaneous circulation from an out-of-hospital cardiac arrest does therapeutic hypothermia (target temperature: 33 C for 48 hours) when compared to therapeutic normothermia (target temperature: 36.8 C) improve the rate of survival with a good neurobehavioral outcome at 12 months?

DESIGN/VALIDITY: This was a well-designed randomized, controlled trial of 260 patients who were randomly assigned to therapeutic normothermia or therapeutic hypothermia. The study had minimal validity concerns; the length of therapeutic hypothermia was 120 hours which is longer than prior trials, and the patients were assigned to their therapy groups within 6 hours after ROSC. The proportion of survivors with VABS-II scores of 70 or more at 12 months, change in VABS-II score from baseline to 12 months, and mortality at 12 months were compared between the two groups. The efficacy analysis for the primary outcome was performed with the use of a pre-specified modified intention-to-treat approach. A subgroup analysis of patients with and without preexisting conditions may have been helpful.

PRIMARY RESULTS: The proportion of survivors with VABS-II scores of 70 or more at 12 months was not significantly different between the two groups (Hypothermia: 19.6%, Normothermia: 12.3%, absolute risk difference: 7.3%, 95% CI (-1.5, 16.1%). The authors specified a clinical significant difference of 20% in their sample size determination. Whether a 7.3% improvement in VABS-II score is clinically significant and the study was underpowered is unclear. It should be noted that a VABS-II score of > 70 is a relatively low bar. The VABS score has a mean of 100 with a standard deviation of 15. A score of 70 (2 standard deviations below the mean) would be higher than only 5% of a normally distributed population. 33% of survivors in the hypothermia group and 38% of survivors in the normothermia group had a decrease in VABS-II score of > 30%.

The secondary outcomes of change in the VABS-II score from baseline to 12 months (P = 0.13). and survival at 1 year (Hypothermia: 38%, Normothermia 29%; P = 0.13) did not differ significantly between the groups. However, there was a statistically significant lower survival time (Hypothermia 149 ±14 days, Normothermia 119 ±14 days p=0.04).

APPLICABILITY: The inclusion of 38 pediatric center in the U.S. and Canada likely make the study's result generalization to those meeting the study's inclusion and exclusion criteria.

AUTHOR'S CONCLUSION: "In conclusion, in comatose children who survive of out-of-hospital cardiac arrest, therapeutic hypothermia, as compared with therapeutic normothermia, did not confer a significant benefit with respect to survival with good functional outcome at 1 year. Survival at 12 months did not differ significantly between the treatment groups."

POTENTIAL IMPACT: We do not often care for pediatric out-of-hospital cardiac arrest with return of spontaneous circulation but when we do, it is useful to know that therapeutic hypothermia has no statistically significant benefits. However, further study is needed to determine the clinical importance of a statistically significant longer survival times in children with therapeutic hypothermia.

The 2015 American Heart Association Pediatric Advance Life Support Guidelines for post resuscitation care (PubMed ID: 26473000) recommend that “for infants and children remaining comatose after out of hospital cardiac arrest, it is reasonable either to maintain 5 days of continuous normothermia (36°C to 37.5°C) or to maintain 2 days of initial continuous hypothermia (32°C to 34°C) followed by 3 days of continuous normothermia.” “Continuous measurement of temperature during this time period is recommended”. “Fever (temperature 38°C or higher) should be aggressively treated after return of spontaneous circulation.”

SEPTIC SHOCK:
ANTIBIOTIC TIMIMG

In pediatric patients with severe sepsis or septic shock is the time from sepsis recognition until antimicrobial administration or appropriate antimicrobial administration associated with an increase in pediatric ICU mortality and the number of days of organ dysfunction?

Michael Mojica, MD
June 2018

Weiss SL, Fitzgerald JC, Balamuth F, Alpern ER, Lavelle J, Chilutti M, Grundmeier R, Nadkarni VM, Thomas NJ.

DELAYED ANTIMICROBIAL THERAPY INCREASES MORTALITY AND ORGAN DYSFUNCTION DURATION IN PEDIATRIC SEPSIS

Crit Care Med. 2014 Nov;42(11):2409-17
PubMed ID: 25148597

STUDY DEFINITIONS	
POPULATION	Inclusion: Pediatric patients 1. Entry into sepsis registry based on sepsis or septic shock consensus criteria a. ≥ 2 aged based systemic inflammatory response criteria b. Confirmed or suspected infection c. Cardiovascular dysfunction (required for septic shock), acute respiratory distress syndrome criteria, or ≥ 2 organ system disfunction 2. Recognition and initial therapy for sepsis in the ED, OR, PICU or inpatient unit Exclusion: 1. Transfer patients: Timing of interventions not consistently available 2. If a patient had more the 1 episode of sepsis only the last episode included Setting: Single Children's Hospital Pediatric ICU (U.S.), 2/2012-1/2013
EXPOSURE	1. Antimicrobial administration (antibiotics, antivirals, antifungals) 2. Appropriate antimicrobial administration defined as: a. All identified organisms sensitive b. If no organism identified antimicrobials followed guideline for likely cause
NO EXPOSURE	Time of sepsis recognition defined as: 1. ED: Triage time 2. Non-ED: Time of first sepsis related intervention (physician order for antimicrobials, blood culture, intravenous fluid bolus, transfer to PICU)
OUTCOME	Primary Outcome: PICU Mortality Secondary Outcomes: 1. PICU length of stay from time of sepsis recognition 2. Sepsis recognition until 28 days a. Vasoactive free days: Dopamine >5 mcg/kg/min. Any Epi, NE, Phenylephrine, Vasopressin, Milrinone b. Ventilator free days: Invasive or non-invasive mechanical ventilation c. Organ failure free days: Any organ system dysfunction 1. Pediatric Index of Mortality Score (PIM-2) 2. Pediatric Logistic Organ Dysfunction Score
DESIGN	Observational: Retrospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	Unclear. Characteristics of the study cohort are presented in table 1. However, characteristics of patients based on time of antimicrobial administration were not presented. The study used both multiple logistic regression and propensity scoring for the primary outcome to account for potential confounding variables. The study used multiple logistic regression for the secondary outcomes to account for potential confounding variables.
Were the circumstances and methods for detecting the outcome similar?	Patients were identified from an institutional sepsis registry. Variables included: “demographics, comorbid conditions, source of infection, microbiology, laboratory results, antimicrobial administration, treatment on the institution’s clinical pathway for management of severe sepsis and septic shock, mechanical ventilation, use of vasoactive infusions, PICU length of stay (LOS), and vital status at PICU discharge”
Was follow-up sufficiently complete?	Yes for the primary outcome but unclear for the secondary outcomes. The primary outcome was PICU mortality and all patient were followed until death or discharge from the PICU. The secondary outcomes were the number of days free of vasoactive infusion, mechanical ventilation and organ dysfunction from sepsis recognition until 28 days. The number of patient who were available for follow up until 28 days was not reported though none of the study outcomes could have occurred after this time.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

Demographic data:
N = 130, 27 (21%) with sepsis, 103 (79%) with septic shock
Location of initial treatment: ED 64 (49%), Inpatient 66 (51%)
Infection source identified: 83%
PICU Mortality: 12.3% (16/130) (14 directly attributed to sepsis, 2 hastened by sepsis (CLD))
: Appropriate: 12% (12/101), Inappropriate: 14% (4/29): p=0.76
Antimicrobials: Antibiotics (100%), antivirals (6%), antifungals (5%)
Appropriate antimicrobials: 78%

TIMING TO ANTIMICROBIAL ADMINISTRATION (MINUTES (MEDIAN, IQR))			
	ALL	ED	NON-ED
Initial Antimicrobials	140 min (77, 277)	123 min (67, 180)*	214 min (78, 678)*
Clinical pathway used	101 min (64, 157)		
Clinical pathway not used	181 min (75, 443)		
Appropriate Antimicrobials	177 min (90, 550)		
*Longer time in Non-ED patients due to delay in time from order to administration			

Propensity Score (3 hours/> 3 hours): OR 3.83, 95% CI (1.06, 13.82)

PICU MORTALITY (TABLE 5,6): UNADJUSTED ODDS RATIO (95% CI)		
Comparison	Initial Antimicrobials	Appropriate Antimicrobials
(1 hour/> 1 hour)	1.67 (0.37, 7.91)	0.98 (0.20, 4.78)
(2 hours/> 2 hours)	2.43 (0.74, 7.99)	2.34 (0.63, 8.71)
(3 hours/> 3 hours)	3.92 (1.2, 12.06)	3.58 (1.09, 11.76)
(4 hours/> 4 hours)	3.60 (1.23, 10.52)	2.86 (0.97, 8.42)
GREEN = Statistically significant difference, RED = No statistically significant difference		

PICU MORTALITY (FIGURE 1)	
ALL	12.3%
0-1 hour	8.3%
1-2 hours	6.5%
2-3 hours	4.3%
> 3 hours	21.2%

Secondary Outcomes (Table 9): PICU LOS, Free-days (vasoactive, organ dysfunction, ventilation)
Initial Antimicrobials (<=3 hours/> 3 hours): Difference in organ dysfunction free days only
Appropriate Antimicrobials (<=3 hours/> 3 hours): No difference in any secondary outcomes

HOW PRECISE IS THE ESTIMATE OF THE RISK?

Confidence intervals for the unadjusted odds ratios are presented above. Confidence intervals are wide given the small number of total patients (n=130) and with PICU mortality (n=16)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Yes. The study was conducted in a single children's hospital pediatric ICU. This was a predominantly white population (49%) and 59% had 1 or more preexisting conditions. 74% required a vasoactive infusion and 62% required mechanical ventilation. Compliance with non-antimicrobial intervention goals was limited (e.g. initial fluid bolus < 20 minutes (17%), < 60 minutes (35%), lactate measured (71%)).
Was follow-up sufficiently long?	Yes. The primary outcome was PICU mortality. The authors chose this outcome because death after PICU discharge is likely is not dependent on initial management. Secondary outcomes were measured for 28 days after time of sepsis recognition.
Is the exposure similar to what might occur in my patient?	Yes. Current recommendations are for administration of antimicrobials within 1 hour of sepsis recognition.
What is the magnitude of the risk?	There was a significantly increased risk of PICU mortality in patients receiving antimicrobials after 3 hours (21.2%) compared to 1 hour (8.3%), 1 to 2 hours (6.5%) and f 2 to 3 hours (4.3%).
Are there any benefits that offset the risks associated with exposure?	Yes. The benefit of antibiotics in treating infection is clear. Risks may include allergic reactions and predisposition to subsequent infections with resistant organisms. There is a clear benefit to risk ratio in patients with sepsis.

CLINICAL BOTTOM LINE

BACKGROUND: First-hour recommendations of the pediatric 2017 guideline update include: sepsis recognition, establishing intravenous access and initiating intravenous fluids and resuscitation as needed, administering antibiotics, and starting vasoactive agents if needed (ACCCM, Critical Care 2017, PubMed ID: 28509730). The recommendation for administration of antimicrobials within 1 hour of sepsis recognition is based primarily on adult data which suggests a decrease in sepsis survival by 7.6% per hourly delay (Kumar, Critical Care Med 2006, PubMed ID: 16625125).

CLINICAL QUESTION: In pediatric patients with severe sepsis or septic shock is the time from sepsis recognition until antimicrobial administration or appropriate antimicrobial administration associated with an increase in pediatric ICU mortality and the number of days of organ dysfunction?

DESIGN/RISK OF BIAS: This was a retrospective cohort study utilizing data from a sepsis registry from pediatric patients meeting consensus criteria for sepsis or septic shock admitted to a single children's hospital pediatric ICU. Characteristics of patients based on time of antimicrobial administration were not presented. The study used both multiple logistic regression and propensity scoring for the primary outcome to account for potential confounding variables. The study used multiple logistic regression for the secondary outcomes to account for potential confounding variables. The retrospective cohort design is susceptible to bias intrinsic to the nature of observation studies. More important for this study question is that the reason for delay in antimicrobial after sepsis recognition are unknown. The time from order to administration was significantly longer for non-emergency department patients.

The primary interventions of interest were the time from sepsis recognition to the administration of initial antimicrobial (antibiotics, antivirals, or antifungals) and form sepsis recognition to administration of "appropriate" antimicrobials administration defined as: coverage of identified organisms or if no organism was identified antimicrobial selection followed institutional guidelines for likely cause. Two different definitions of time of sepsis recognition were utilized. For ED patients the triage time was considered sepsis recognition and for non-ED the time of first sepsis related intervention (physician order for antimicrobials, blood culture, intravenous fluid bolus, transfer to PICU) was utilized. It seems somewhat arbitrary to begin the sepsis clock at these times though sepsis metrics often use the ED definition. It is unclear why abnormal vital signs were not used for non-ED patients.

The primary outcome was pediatric ICU mortality. The authors indicate that they chose this time to eliminate deaths after this time that were unlikely to be related to initial interventions for sepsis. Secondary outcomes included pediatric ICU length of stay from time of sepsis recognition and vasoactive infusion, mechanical ventilation and organ failure free days until day 28 after sepsis recognition.

PRIMARY RESULTS: The primary analysis included 130 patients of which 12.3% (16) had in PICU mortality. 27 (21%) patients were categorized as sepsis and 103 (79%) as septic shock. Antibiotics were administered in 100% or patients, antivirals in 6% and antifungals in 5%. Appropriate antimicrobials were administered in 78% of patients. There was no significant difference in ICU mortality in those with initial antimicrobials (12% (12/101)) and inappropriate antimicrobials (14% (4/29), p=0.76).

The median time to initial antibiotics was 140 min, IQR (77, 277 minutes), and to appropriate antibiotics was 177 min, IQR (90, 550 minutes). Both of these exceed the recommendation of antimicrobials in the first hour of care. There was a statistically significant higher odds of PICU mortality in those receiving antimicrobials after 3 hours compared to those less than or equal to 3 hours for both the initial and appropriate antimicrobials (see table below). A separate propensity match analysis demonstrated a similar increased association (Odd Ratio: 3.83, 95% CI (1.06, 13.82)). There was also a significantly increased absolute risk of PICU mortality in patients receiving antimicrobials after 3 hours (21.2%) compared to less than hours 1 hour (8.3%), 1 to 2 hours (6.5%) and from 2 to 3 hours (4.3%).

PICU MORTALITY (TABLE 5,6): ANTIMICROBIAL ADMINISTRATION TIMING		
COMPARISON	INITIAL ABX	APPROPRIATE ABX
(1 hour/> 1 hour)	1.67 (0.37, 7.91)	0.98 (0.20, 4.78)
(2 hours/> 2 hours)	2.43 (0.74, 7.99)	2.34 (0.63, 8.71)
(3 hours/> 3 hours)	3.92 (1.2, 12.06)	3.58 (1.09, 11.76)
(4 hours/> 4 hours)	3.60 (1.23, 10.52)	2.86 (0.97, 8.42)
GREEN = Statistically significant difference, RED = No statistically significant difference		

For the secondary outcomes of pediatric ICU length of stay, free-days until 28 days after sepsis recognition of vasoactive infusion, organ dysfunction and mechanical ventilation, there was a significant increase of 4 days in organ dysfunction after 3 hours for initial antimicrobials. There were no significant difference in any of the secondary outcomes for appropriate antibiotics.

APPLICABILITY: The study's results are likely applicable to patients cared for and admitted primarily to a children's hospital and cared for in a pediatric ICU who meet the study's inclusion and exclusion criteria. This was a predominantly white population (49%) and 59% had 1 or more preexisting conditions. 79% were categorized as septic shock, 74% required a vasoactive infusion, and 62% required mechanical ventilation. Generalizability to other settings and other populations is unclear. Surprisingly, compliance with non-antimicrobial intervention goals was limited (e.g. initial fluid bolus < 20 minutes (17%), < 60 minutes (35%), lactate measured (71%)).

AUTHOR'S CONCLUSION: "Delayed antimicrobial therapy beyond 3 hours from sepsis recognition was an independent risk factor for mortality and prolonged organ failure in pediatric severe sepsis and septic shock. In keeping with current guidelines, empiric broad-spectrum antimicrobial therapy should be prioritized in the initial resuscitation of pediatric sepsis. Given the trend toward an escalating risk of mortality with delays of 1 and 2 hours from sepsis recognition to antimicrobial administration, further study is needed to determine the optimal timing of antimicrobial administration in the pediatric population but delays more than 3 hours should be avoided."

POTENTIAL IMPACT: The timely administration of antimicrobials in pediatric sepsis makes clinical sense and is part of current metrics. This study did not provide evidence for the current recommendation of antimicrobial administration within 1 hour of sepsis recognition and instead provides strong support for administration prior to 3 hours. Randomized trials of appropriate antimicrobials could better elucidate the association between timing of antimicrobial administration and pediatric sepsis morbidity and mortality. The authors correctly state that use of clinical pathways, electronic order sets, and guidance and rapid access to appropriate antibiotics may improve time to antimicrobials after sepsis recognition.

SEPTIC SHOCK:
DOPAMINE VS EPINEPHRINE

In children with fluid refractory septic shock does a first line vasoactive infusion of Epinephrine when compared to an infusion of Dopamine decrease 28-day all-cause mortality rate?

Katrina Knapp D.O., Alvira Shah M.D.
August 2015

Ventura AM, Shieh HH, Bousso A, Góes PF, de Cássia F O Fernandes I, de Souza DC, Paulo RL, Chagas F, Gilio AE.

DOUBLE-BLIND PROSPECTIVE RANDOMIZED CONTROLLED TRIAL OF DOPAMINE VERSUS EPINEPHRINE AS FIRST-LINE VASOACTIVE DRUGS IN PEDIATRIC SEPTIC SHOCK.

Crit Care Med. 2015 Nov;43(11):2292-302.
PubMed ID: 26323041

STUDY DEFINITIONS	
POPULATION	Inclusion: 1 month to 15 years, fluid-refractory septic shock defined as persistence of clinical signs of hypoperfusion in spite of a fluid bolus of at least 40 ml/kg of crystalloids or colloids: abnormal heart rate for age, abnormal mental status, systolic BP < 5th % for age, Capillary refill > 2 seconds, weak peripheral pulses with a difference between central and peripheral, cool extremities, and urine output < 1ml/kg/hour (American College of Critical Care / AHA PALS definition) Exclusion: Received vasoactive drugs prior to hospital admission, cardiac disease, prior participation in the trial during the same hospital stay, declined to participate in the trial, do not resuscitate orders Setting: Single Pediatric ICU (Brazil). 1/2009-7/2013
INTERVENTION	Epinephrine 0.1 mcg/kg/min titrated up to 0.3 mcg/kg/min in 20 minute intervals
CONTROL	Dopamine 5 mcg/kg/min titrated up to 10 mcg/kg/min in 20 minute intervals
OUTCOME	Primary Outcome: Death from any cause within 28 days of study entry Secondary Outcomes: 1. Health Acquired Infections: central catheter-associated bloodstream infection, catheter associated urinary tract infection, ventilator associated pneumonia, surgical site infection, nosocomial pneumonia. 2. Need for additional vasoactive infusions 3. Multiple organ dysfunction score.
DESIGN	Interventional: Randomized Clinical Trial

ARE THE RESULTS VALID?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized with a computer generated sequence.
Was randomization concealed?	Yes. It appears that randomization was concealed. A registered nurse who was not involved in the decision making process for the protocol or in reassessment of the patient was responsible for checking the randomization code and accessing password-protected software for the drug prescription. Non-identified vials were prepared but not stated whether similar in color or quantity.
Were patients in the study groups similar with respect to known prognostic factors?	Yes, at baseline patients were similar according to age, gender, nutritional status, disease status (PRISM score and PELOD score), presence of underlying disease, source of infection, and etiology. The number of patients in each group that were hypotensive was not presented or the infectious source of the sepsis. There were 19 patients in the Dopamine group who were labeled as “other” as source of infection and 10 in the Epinephrine group.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Yes. The authors state that the study double-blinded. A registered nurse who was not involved in the decision making protocol or reassessment of the patient knew what drug she was giving to the patient since she prepared the medication. Vials were non-identifiable with the printed prescription kept in a sealed opaque envelope. Physicians were aware of the flow rate, so they could have possibly figured out what drug they were administering based on flow rate. It is not clear whether the physicians knew what 2 drugs were being studied or not. Likely the physicians were blinded to the study group as 33% of patients in the Epinephrine group were given Epinephrine as a rescue agent when they were considered nonresponsive to the study group.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Follow up was complete. All patients that were analyzed in study were followed up to the 28-day follow up.
Were patients analyzed in the groups to which they were randomized?	Yes. The primary analysis was an intention to treat analysis.
Was the trial stopped early	Yes. The sample size determination required 152 patients to detect a 15% difference in mortality. Interim analyses were planned at 60 and 120 patients per group. The 60 patient interim analysis revealed a 15.7% difference and the trial completed enrollment at 120 patients.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

PRIMARY OUTCOME

	ALL-CAUSE MORTALITY (28 DAYS)		
	YES	NO	
EPINEPHRINE	4	53	57
DOPAMINE	13	50	63
	17	103	120

Risk Epinephrine: 4/57 = 7%
Risk Dopamine: 13/63 = 20%
Risk Difference: Dopamine – Epinephrine = 20 – 7 = 13%, 95% CI (1, 25.9%)
Relative Risk = Epinephrine/Dopamine = 7/20 = 0.35, 95% CI (0.12, 0.98)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence interval for risk difference did not include 0 so there was statistically significant difference but the difference was clinically significant difference based on the authors definition of a clinically significant difference of 15% used in the sample size determination.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	It is unknown whether the patients are similar to our patient population. The study was conducted in Brazil so it is unknown what disease pathogens/patterns are present in their population and if antibiotic resistance exists. It is also unclear if Brazil has the same immunizations as the US.
Were all clinically important outcomes considered?	No. The proportion with neurologically intact survival and was not provided.
Are the likely treatment benefits worth the potential harm and costs?	The number need to treat is NNT = 1/ARD = 1/0.13 = 8. For every 8 patients treated with Epinephrine 1 additional patient would avoid death within 28 days when compared to patients receiving Dopamine.

CLINICAL BOTTOM LINE

BACKGROUND: There is little evidence to support the selection of the initial vasoactive infusion to administer in pediatric patients with septic shock. The current American Heart Association (AHA) Pediatric Sepsis Algorithm (2010) recommends Dopamine for normotensive patients; Norepinephrine for hypotensive patients with “warm” shock and Epinephrine in hypotensive patients in “cold” shock. This study aimed to determine the appropriate initial vasoactive infusion in pediatric patients with fluid refractory septic shock.

CLINICAL QUESTION: In children with fluid refractory septic shock does a first line vasoactive infusion of Epinephrine when compared to an infusion of Dopamine decrease 28-day all-cause mortality rate?

DESIGN/VALIDITY: This was a well-designed, double blind, randomized clinical trial that included 120 patients in the primary analysis. Patients in fluid refractory septic shock were randomized to Dopamine or Epinephrine. The starting dose of Dopamine was 5 mcg/kg/min, which was titrated to 10 mcg/kg/min in 20-minute intervals if appropriate clinical response was not achieved. Epinephrine dose was started at 0.1 mcg/kg/min, which was titrated to 0.3 mcg/kg/min in 20-minute intervals if appropriate clinical response was not achieved.

There are a number of validity concerns in the design of this trial. Dopamine may not have been the recommended initial agent in these patients. Since the percentage of patients who were hypotensive was not provided there is no means to determine this. The article states that > 80% of all patients in both groups were in cold shock (Dopamine 88.3%, Epinephrine 70.2%) making it likely that a significant proportion in the Dopamine group were hypotensive. In addition, a starting dose of Dopamine of 5 mcg/kg/min and a maximum dose of Dopamine of 10 mcg/kg/kg is likely insufficient and not comparable to the starting and maximum dose of Epinephrine used in the trial. Dopamine starting at a low dose of 5 mcg/kg/min exhibits more inotropic effects. It is not until doses of greater than 10 mcg/kg/min that Dopamine exhibits more alpha-adrenergic effects. Whereas Epinephrine has alpha-adrenergic effects at all doses used in the trial. Finally, patients in the Dopamine group had a higher heart rate at baseline, were more likely to be in “cold” shock and the vasoactive infusion was initiated approximately on hour later. These issues could bias the results of this study against Dopamine.

PRIMARY RESULTS: The study found that patients in the Epinephrine group were 13% (95% CI 1 to 25.9%) less likely to have death at 28 days compared to the Dopamine group. The number need to treat is NNT = 1/ARD = 1/0.13 = 8. For every 8 patients treated with Epinephrine 1 additional patient would avoid death within 28 days when compared to patients receiving Dopamine.

In the logistic regression analysis, the adjusted odds ratio for 28 day all-cause mortality (Dopamine/Epinephrine) was 6.51, 95% CI (1.12, 37.8). Health care associated infections were higher in the Dopamine group (28.5%) than in the Epinephrine group (2.3%). This was primarily due to ventilator-associated pneumonia. The proportion of non-infectious adverse events was similar.

APPLICABILITY: This was a single center study in a population that may not be similar to ours. The concerns in the study design discussed above bias against Dopamine making the results of the study difficult to apply clinically at this time.

AUTHOR'S CONCLUSIONS: "Further multicenter trials or single-center studies are necessary to verify the reproducibility of our results. The best research scenario would be to control the initial as well as the subsequent catecholamines with priority given to those that do not increase cAMP. The results of our investigation could be useful for countries with similar mortality rates, but if local outcomes are already superior to those observed in our single- center trial, the observed results may not apply. The use of dopamine in this population was associated with increased death and HAI odds ratios. Early administration of peripheral or intraosseous epinephrine was safe and associated with increased survival rates compared with dopamine. Limitations should be observed while interpreting these results."

POTENTIAL IMPACT: Larger, multicenter studies eliminating some of the validity concerns would be required to recommend a change in the current recommendations.

SEPTIC SHOCK:
EARLY GOAL-DIRECTED THERAPY (ADULTS)

In adult patients with early septic shock presenting to the emergency department does early goal-directed therapy when compared to usual care reduce all-cause mortality at 90 days?

Dana Suozzo M.D., Michael Mojica M.D.
October 2014

Peake SL, Delaney A, Bailey M, et al.

GOAL-DIRECTED RESUSCITATION FOR PATIENTS WITH EARLY SEPTIC SHOCK (ARISE TRIAL)

N Engl J Med 371: 1496-1506, October 16, 2014
PubMed ID: 25272316

STUDY DEFINITIONS	
POPULATION	Inclusion: 1. ≥ 18 years, met the eligibility criteria within 6 hours after presentation to the ED were assessed for enrollment 2. Suspected or confirmed infection with 2 or more criteria for systemic inflammatory response syndrome Temp <36 or >38 HR >90, RR > 20 or partial pressure of arterial CO_2 <22 mmHg or requirement for invasive mechanical ventilation, WBC >12 or <4 or >10% immature bands. 3. Refractory hypotension: Systolic BP <90mmHg, MAP <65 after IVF challenge (>1L within 60 minutes) 4. Refractory hypoperfusion. Blood lactate level of 4.0mmol/L or more Exclusion 1. <18 years 2. Contraindication to central venous catheter insertion in the superior vena cava 3. Contraindication to receiving blood products 4. Hemodynamic instability due to active bleeding 5. Underlying disease process with life expectancy < 90 days 6. Death deemed imminent & inevitable 7. Documented limitation of therapy or restricting implementation of the study protocol or aggressive care deemed unsuitable by treating clinician 8. In-patient transfer from another acute health care facility 9. Confirmed or suspected pregnancy 10. Inability to commence EGDT within 1 hour or deliver EDGT for 6 hours Setting: 51 tertiary, non-tertiary, and rural hospitals (Australia, New Zealand), 10/2008–4/2014
INTERVENTION	Early Goal-directed Therapy: Care bundle (vasopressors, IVF, arterial and venous catheters capable of continuous ScvO2 measurement)
CONTROL	Usual Care: Treatment decisions by clinical care for location of care delivery investigations, monitoring and treatment. $SCVO_2$ monitoring not permitted
OUTCOME	Primary Outcome: Death by day 90 Secondary 1. Mean duration of stay (ED, ICU, Hospital) 2. Use & duration of organ support (Invasive mechanical ventilation, duration of ventilation, vasopressor support, duration of vasopressor support, renal-replacement therapy, duration of renal-replacement therapy) Tertiary 1. Death by day 28 2. Death by time of discharge from ICU 3. Death by time of discharge from hospital
DESIGN	Interventional: Randomized Clinical Trial

ARE THE RESULTS VALID?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Eligible patients were randomly assigned in a 1:1 ratio to receive either early goal-directed therapy (EGDT) or usual care for 6 hours after presentation to ED. Randomization was stratified by study center using permuted-block method & performed by a centralized telephone interactive voice-response system.
Was randomization concealed?	No, both clinicians and patients were aware of study-group assignments though it appeared that there was no way to bias allocation to the treatment group.
Were patients in the study groups similar with respect to known prognostic factors?	Yes, the experimental and control groups had similar demographic and clinical characteristics. The criterion for refractory hypotension, elevated lactate level, and the median time to presentation to the emergency department were similar in both groups.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study was not blinded.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Only 1 of the 792 patients who received EDGT and 1 of the 796 patients who received usual care were lost to follow-up.
Were patients analyzed in the groups to which they were randomized?	Yes. An intention to treat analysis included all enrolled patients for which data was available. No assumptions were made for missing or unavailable data.
Was the trial stopped early	No.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

	DEATH		
	YES	NO	
EARLY GOAL DIRECTED THERAPY (EGDT)	147	645	792
USUAL CARE (UC)	150	646	796

Risk of Death (EGDT): 147/792 = 18.6%
Risk of Death (UC): 150/796 = 18.8%
Risk Difference: 18.8 – 18.6 = 0.2%, 95% CI (-3.6, 4.0%)
Relative Risk: 18.8/18.6 = 1.02, 95% CI (0.8, 1.2)

Other than a 10% greater use of vasopressor support in the EGDT group, there were no statistically significant differences in the secondary and tertiary outcome measures (Table 2).

There were no statistically significant differences in the survival analysis and subgroup analysis (Figure 2a, 2b)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Relative Risk: 0.985, 95% CI (0.8, 1.2)
Risk Difference: 0.28%, 95% CI (-3.6, 4.0%)

The study had a power of 85 to 90% to detect an absolute risk reduction of 7.6% in the primary outcome. The absolute risk difference (ARD) is 0.28% The confidence interval includes 0% indicating the difference is not statistically significant. The 0.28% difference is less than the 7.6% the authors considered a clinically significant difference.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Partially. Although the age range of most the patients in the study is older than the population we serve; the characteristics, inclusion criteria, and interval presentation to the ED are similar. Most patients in the study live in a home setting versus long-care facilities. Vasopressor use, SBP, and lactate levels were also similar. The total volume of fluid used per patient is greater then that used in a pediatric population, but the actual volume per weight (~35 ml/kg) is less than the 60 ml/kg in pediatric resuscitation.
Were all clinically important outcomes considered?	Yes. The significant outcomes related to EGDT vs. usual care in the setting of sepsis were considered in not only primary outcome, but also secondary, tertiary outcomes.
Are the likely treatment benefits worth the potential harm and costs?	No. The number needed to treat stated in the study is 352 (-28, 24). With similar adverse events in both the EDGT and the usual care group, adoption of this treatment strategy does prevent the primary outcome of all cause death by day 90.

CLINICAL BOTTOM LINE

BACKGROUND: In 2011, Emanual Rivers published his landmark study (Rivers, NEJM 2011, PubMed ID: 11794169) demonstrating a 16% decrease in in-hospital mortality in adults in septic shock using early goal directed therapy. (EGDT). EGDT included a 6-hour resuscitation bundle recommended by the surviving sepsis campaign. The bundle includes: early recognition of septic shock, control of source infection including early administration of antibiotics and resuscitation with intravenous fluids and vasoactive infusions to specific physiologic targets. These targets required invasive monitoring of central venous pressure (CVP) and central venous oxygen saturation ($SCV0_2$) via a central line. Concerns have arisen about:

1. The external validity of the River's study: n = 263 total, conducted at a single center and utilization of a proprietary catheter to measure $SCVO_2$
2. The efficacy and risks associated with individual elements of the sepsis bundle
3. The infrastructure and resource requirements of the bundle

The recently published PROCESS trial in 31 centers in the United States including 1,341 patients (Yealy, NEJM 2014, PubMed ID: 24635773) did not identify an improvement in all-cause mortality at 60 days for protocol based EGDT.

CLINICAL QUESTION: In adult patients with early septic shock presenting to the emergency department does early goal-directed therapy when compared to usual care reduce all-cause mortality at 90 days?

DESIGN/RISK OF BIAS: This multicenter ARISE Trial (the Australasian Resuscitation In Sepsis Evaluation) was designed to compare the effect of early-goal directed therapy versus usual care on all-cause mortality at 90 days in the setting of early sepsis in adult patients presenting to the emergency department. (n = 1,600). The primary risk of bias concern is that since the introduction of the surviving sepsis campaign the "usual care" may have evolved to include elements of the sepsis bundle. Central venous catheters were placed in 62% of the usual care group though none received $SCVO_2$ monitoring. Patients in the usual care group received vasopressor support 10.5 % less frequently than patients in the EGDT group (76.3% - 65.8%).

In addition, it is important to determine if the EGDT group received all of the interventions required of the sepsis bundle. Only 2.3% of the group had EGDT stopped primarily because of requiring an operation or transfer to another institution. EGDT target goals were met within 6 hours for: O_2 saturation (99.6%), $SCVO_2$ (95.3%), MAP (94.1%) and CVP (88.9%).

PRIMARY OUTCOME: Total deaths in the EDGT group were 147/792 (18.6%), compared to 150/796 (18.8%) deaths in the usual care group despite patients in the EGDT group receiving more intravenous fluids and more vasoactive infusions. There was also no difference in the primary outcome in any of the predefined subgroups. In addition, there was no notable difference between the groups in regard to the length of hospital stay, survival time, in-hospital mortality, and duration of organ support. (Table 2, Figure 2b). Death occurred most often within the first 10 days of randomization and did not change appreciably after 30 days (Figure 2a).

AUTHOR'S CONCLUSION: "The results of our trial show that EGDT, as compared with usual resuscitation practice, did not decrease mortality among patients presenting to the emergency department with early septic shock. Our findings suggest that the value of incorporating EGDT into international guidelines as a standard of care is questionable."

POTENTIAL IMPACT: This study was a well-designed study that addressed the validity concerns of a trail with both a complex intervention and control. With no major differences in outcome, it does not demonstrate that EDGT is superior to usual care in emergency department adult patients with early sepsis.

SEE ALSO: 2017 Meta-Analysis of the ARISE, PROCESS and PROMISE Trials

PRISM Investigators, Rowan KM, Angus DC, Bailey M, Barnato AE, Bellomo R, Canter RR, Coats TJ, Delaney A, Gimbel E, Grieve RD, Harrison DA, Higgins AM, Howe B, Huang DT, Kellum JA, Mouncey PR, Music E, Peake SL, Pike F, Reade MC, Sadique MZ, Singer M, Yealy DM.
Early, Goal-Directed Therapy for Septic Shock:A Patient-Level Meta-Analysis.
N Engl J Med. 2017 Jun 8;376(23):2223-2234., PubMed ID: 28320242

SEPTIC SHOCK:
ED IDENTIFICATION PROCESS

In pediatric patients presenting to the emergency department does an electronic sepsis alert process completed by nursing which includes
1. Tachycardia OR Hypotension &
2. Fever OR Hypothermia OR Concern for infection &
3. Capillary refill > 2 seconds OR altered mental status OR a high risk medical condition
which when positive triggers a bedside clinical assessment by a pediatric emergency medicine faculty or fellow, accurately identify severe sepsis or septic shock as defined by activation of a sepsis protocol in the ED or transfer to the pediatric ICU within 24 hours of presentation?

Michael Mojica, MD
March 2018

Balamuth F, Alpern ER, Abbadessa MK, Hayes K, Schast A, Lavelle J, Fitzgerald JC, Weiss SL, Zorc JJ.

IMPROVING RECOGNITION OF PEDIATRIC SEVERE SEPSIS IN THE EMERGENCY DEPARTMENT: CONTRIBUTIONS OF A VITAL SIGN–BASED ELECTRONIC ALERT AND BEDSIDE CLINICIAN IDENTIFICATION

Ann Emerg Med. 2017 Dec;70(6):759-768.e2.
PubMed ID: 28583403

STUDY DEFINITIONS	
POPULATION	Inclusion: All patients presenting to the ED Exclusion: Transferred patients administered antibiotics prior to ED arrival Setting: Single Children's Hospital, 6/2013-5/2014 (pre), 6/2014-5/2015 (post)
TEST	Electronic Alert: Based on AAP Pediatric Septic Shock Collaborative (appendix) Move to next stage if any parameter positive. 1. Age based Tachycardia or Hypotension (based on institution early warning score) (See appendix) 2. Fever (≥ 38 C at home or in ED) or Hypothermia or Signs/Symptoms of infection 3. Capillary refill > 2 seconds or Altered mental status or High risk medical condition (See appendix) ≥ 1 parameter required at each of the stages to trigger a bedside clinical huddle Sepsis Huddle: Nurse, PEM faculty or PEM fellow. Bedside decision whether to activate pediatric sepsis pathway in the ED
REFERENCE STANDARD	Treatment of Severe Sepsis 1. ED activation of sepsis protocol 2. Development of severe sepsis/septic shock requiring ICU admission within 24hr
OUTCOME	1. Test characteristics of electronic sepsis alert process (triage tool and huddle) Sensitivity Analysis a. Over treatment: Excluding patients treated with the sepsis pathway who did not require pediatric ICU care within 24 hours of ED stay. b. Including only patients requiring vasoactive agents 2. Proportion of patients appropriately treated in the ED pre and post protocol Missed case: Any patient with severe sepsis who was not treated with ED sepsis clinical protocol and order set.
DESIGN	Prospective cohort: A pre/post intervention quality improvement initiative

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. The sample represented all patient presenting to the ED of a Children's hospital ED with a census of > 90,000 patients per year. This likely represents a patient population with a high proportion of at risk medical conditions.
Did investigators compare the test to an appropriate, independent reference standard?	Unclear. The reference standard was activation of a sepsis protocol in the ED or subsequent transfer to the ICU for severe sepsis. The problem with ED activation is that it is based on the parameters of the triage process (the reference standard is not independent of the test). If for example, more activations occurred in patients who were febrile with poor perfusion and a high risk medical condition then the accuracy of the triage process would be falsely elevated. The test in this study is a composite test consisting on many parameters. The contribution of each parameter to test accuracy was not presented.
Were those interpreting the test and reference standard blind to the other results?	No. Those assessing the reference standard were aware of the study parameters in making their decision. The interpretation of the electronic triage parameters was completed prior to sepsis protocol activation.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	No. The study reference standard was activation of a sepsis protocol in the ED or subsequent transfer to the ICU for severe sepsis. There was no objective clinical or laboratory confirmation of severe sepsis and these two references standards may not be equivalent. The authors attempted to account for over treatment (patients who had the sepsis protocol activated but may not have needed it) by performing two sensitivity analyses including only patients admitted to the ICU and only patients who were administered a vasoactive agent.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

ED visits (pre-intervention): 86.037
ED visits (post-intervention): 96,472

Severe sepsis:
0.34% (326/96,472) assuming all ED protocol activation had sepsis
0.20% (196/96,472) assuming only patients admitted to the ICU had sepsis

Electronic Sepsis Alert (ESA) Positive: 1.2% (1,112/96,472) 1 in every 87 patients
Electronic Sepsis Alert Positive and Huddle Positive: 0.27 (265/96,472) 1 in every 364 patients
or 23.8% (265/1,112) or 1 in every 3.4 patients with a positive electronic sepsis alert

TEST CHARACTERISTICS: SEPSIS ALERT POSITIVE[1] ONLY

	ALL	ICU ADMIT[2]	VASOACTIVE ONLY[2]
Sensitivity	86.2% (82, 89.5%)	77% (70.5, 82.7%)	83.9% (66.2, 94.6%)
Specificity	99.1% (99, 99.2%)	99% (98.9, 99.1%)	98.9% (98.9, 99%)
Predictive Value (+)	25.4% (22.8, 28.0%)	13.6% (11.7, 15.8%)	2.4% (2.0, 2.8%)
Predictive Value (-)	100% (99.9, 100%)	100% (99.9, 100%)	99.9% (99.9, 100%)
Likelihood Ratio (+)	100.2 (92.6, 108.6)	77.5 (70.2, 85.6)	75.1 (63.7, 88.6)
Likelihood Ratio (-)	0.14 (0.11, 0.18)	0.23 (0.2, 0.3)	0.16 (0.07, 0.36)

1. Sepsis alert protocol activate in ED or transfer to ICU for severe sepsis/septic shock in 24 hrs
2. Sensitivity analyses to account for possibility of over activation of sepsis protocol in the ED

TEST CHARACTERISTICS: SEPSIS ALERT POSITIVE[1] OR CLINICIAN IDENTIFIED[3]

	ALL	ICU ADMIT[2]	VASOACTIVE ONLY[2]
Sensitivity	99.4% (78.8, 99.8%)	99% (96.4, 99.9%)%)	95.1% (83.5, 99.4%)
Specificity	99.1% (99.1, 99.2%)	99% (98.9, 99.1%)	98.9% (98.8, 99.0)
Predictive Value (+)	28.5% (25.9, 31.2%)	16.9% 916, 17.8%)	3.5% (3.2, 3.8)
Predictive Value (-)	100% (99.9, 100%)	100 (99.9, 100%)	100% (99, 100%)
Likelihood Ratio (+)	115.6 (107.9, 103.7)	99.6 (93.3, 106.2)	85.5 (78, 93.6)
Likelihood Ratio (-)	0.01 (0.00, 0.02)	0.01 (0.00, 0.04)	0.05 (0.01, 0.19)

1. Sepsis alert protocol activate in ED or transfer to ICU for severe sepsis/septic shock in 24 hrs
2. Sensitivity analyses to account for possibility of over activation of sepsis protocol in the ED
3. Sepsis alert negative (triage tool and huddle) and identified independently by clinicians

Missed Patients: Pre-intervention: 17%, Post-intervention 4%

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Unclear. Inter-rater reliability of the electronic triage process parameters and the clinical huddle were not reported. There are elements of the triage process that are objective (e.g. fever and hypotension) but also elements that are subjective. These include those that require clinical judgment such as the assessment of whether there are signs and symptoms of infection in the afebrile patient and whether the patient has an altered mental status. This ED has approximately 3 sepsis activations a day and the nurses may have considerable experiences in answering these questions. This may not be generalizable to non-children's hospital settings. In addition, the process for determining sepsis protocol activation from the bedside huddle is not clearly delineated. It would have been helpful to determine if there is a difference in accuracy between PEM faculty and fellows.
Are the study results applicable to the patients in my practice?	The study population represents a single Children's hospital. Table 1 only includes age, gender and ED disposition. A table with the proportion of patients meeting each of the electronic triage alert criteria would have been helpful. In particular, I would like to have seen the proportion with a high risk medical condition.
Will the test results change my management strategy?	Not at present. All of the information required to implement this system is not yet available (e.g. the vitals sign cutoffs utilized). It would be helpful to validate the process in a multicenter study including both children's hospital and community ED.
Will patients be better off as a result of the test?	Yes. A greater number of patients with sepsis were identified after the intervention. The number of patients requiring a sepsis huddle prior to the intervention was not presented.

CLINICAL BOTTOM LINE

BACKGROUND: Severe sepsis and septic shock are a major cause of pediatric morbidity and mortality, and the pediatric section in Surviving Sepsis clinical guidelines reiterate adult studies suggesting that early recognition, fluid resuscitation, and antibiotics are mortality-reducing measures. Systemic inflammatory response system (SIRS) vital signs have been found to be neither sensitive nor specific in children. Scott (Academic EM 2015, PubMed ID: 25778743) analyzed the prevalence and test characteristics of SIRS vital signs in children presenting to a single children's hospital ED. SIRS vital signs were defined as a fever with elevation of at least one other vital sign. 15% of non-trauma patients met SIRS vital signs criteria while only 0.25% required a critical care intervention (intubation or use of a vasoactive infusion within 24 hours of the ED visit). 82% of those with SIRS vital signs were discharged from the ED. More importantly, SIRS vital signs identified only 23%, 95% CI (16-33%) of those requiring a critical care intervention. The 2017 pediatric surviving sepsis guidelines acknowledge that there is insufficient evidence to endorse a specific sepsis trigger tool and recommend that each institution develop their own recognition bundle (Amer College Critical Care, Critical Care Medicine 2017, PubMed ID: 28509730).
An identification process should be both sensitive to rapidly identify and treat all patients with sepsis and specific so as to not overburden the ED with false alerts.

CLINICAL QUESTION: In pediatric patients presenting to the emergency department does an electronic sepsis alert process completed by nursing which includes:
1. Tachycardia OR Hypotension AND
2. Fever OR Hypothermia OR Concern for infection AND
3. Capillary refill > 2 seconds OR Altered Mental Status OR a High Risk Medical Condition
which when positive triggers a bedside clinical assessment by a pediatric emergency medicine faculty or fellow, accurately identify severe sepsis or septic shock as defined by activation of a sepsis protocol in the ED or transfer to the pediatric ICU within 24 hours of presentation?

DESIGN/RISK OF BIAS: This was a prospective cohort including all ED patients (n = 96,472 in the post intervention phase) over a year assessing the test characteristics of an electronic sepsis alert triage tool in conjunction with a bedside clinical assessment. The electronic triage tool was constructed based on an AAP Pediatric Septic Shock Collaborative triage tool.

The primary validity concern is that the activation of an ED sepsis protocol served as a surrogate outcome for severe sepsis and sepsis shock. The study reference standard was activation of a sepsis protocol in the ED or subsequent transfer to the ICU for severe sepsis. There was no objective clinical or laboratory confirmation of severe sepsis and these two references standards may not be equivalent. The authors conducted to sensitivity analyses to address the possibility of over treatment of patients that did not have sepsis. This included a sub-analysis of only patients admitted to the ICU admission and a separate analysis of only patients administered a vasoactive infusion.

The assessment of mental status was described in the text but does not appear in any of the screen shots from the electronic medical record, The authors state that the mental status assessment "is completed as part of standard triage assessment and automatically incorporated into the logic of the alert .....The mental status assessment is a drop-down menu completed by the triage nurse that is dichotomized by our algorithm into normal or abnormal". This is an important consideration given that this assessment may be difficult in patients who do not have a normal mental status at baseline.

PRIMARY RESULTS: 0.34% (326/96,472) of all patients had sepsis if you assume that all protocol activation patients had sepsis and 0.20% (196/96,472) had sepsis if you assume that only patients admitted to the ICU had sepsis. 1.2% (1,112/96,472) or 1 in every 87 patients had a positive electronic sepsis alert that prompted a bedside huddle. 23.8% (265/1,112) or 1 in every 3.4 patients with a positive electronic triage screen and huddle had the sepsis protocol activate in the ED. There was a decrease in the proportion of missed patients from 17% pre-intervention to 4% post-intervention. The proportion of patient requiring a sepsis huddle in the pre-intervention phase was not presented.

The sensitivity of the alert process including both the electronic triage tool and a bedside clinical assessment was 86.2% (82, 89.5%). That sensitivity decreases when only patients admitted to the ICU (77% (70.5, 82.7%)) or those who received vasoactive infusions (83.9% (66.2, 94.6%) are defined as having sepsis (Table 1). The specificities under all of these conditions were greater than 98.9%. The sensitivities improved to 99.4% (78.8, 99.8%) when patients who were screen negative but were nonetheless identified by clinicians are included (Table 2).

TABLE 1: TEST CHARACTERISTICS: SEPSIS ALERT POSITIVE[1] ONLY

	ALL	ICU ADMIT[2]	VASOACTIVE ONLY[2]
Sensitivity	86.2% (82, 89.5%)	77% (70.5, 82.7%)	83.9% (66.2, 94.6%)
Specificity	99.1% (99, 99.2%)	99% (98.9, 99.1%)	98.9% (98.9, 99%)
Predictive Value (+)	25.4% (22.8, 28.0%)	13.6% (11.7, 15.8%)	2.4% (2.0, 2.8%)
Predictive Value (-)	100% (99.9, 100%)	100% (99.9, 100%)	99.9% (99.9, 100%)
Likelihood Ratio (+)	100.2 (92.6, 108.6)	77.5 (70.2, 85.6)	75.1 (63.7, 88.6)
Likelihood Ratio (-)	0.14 (0.11, 0.18)	0.23 (0.2, 0.3)	0.16 (0.07, 0.36)

1. Sepsis alert protocol activate in ED or ICU for severe sepsis/septic shock within 24 hours
2. Sensitivity analyses to account for possibility of over activation of sepsis protocol in the ED

TABLE 2: TEST CHARACTERISTICS: SEPSIS ALERT POSITIVE[1] OR CLINICIAN IDENTIFIED[3]

	ALL	ICU ADMIT[2]	VASOACTIVE ONLY[2]
Sensitivity	99.4% (78.8, 99.8%)	99% (96.4, 99.9%)%)	95.1% (83.5, 99.4%)
Specificity	99.1% (99.1, 99.2%)	99% (98.9, 99.1%)	98.9% (98.8, 99.0)
Predictive Value (+)	28.5% (25.9, 31.2%)	16.9% 916, 17.8%)	3.5% (3.2, 3.8)
Predictive Value (-)	100% (99.9, 100%)	100 (99.9, 100%)	100% (99, 100%)
Likelihood Ratio (+)	115.6 (107.9, 103.7)	99.6 (93.3, 106.2)	85.5 (78, 93.6)
Likelihood Ratio (-)	0.01 (0.00, 0.02)	0.01 (0.00, 0.04)	0.05 (0.01, 0.19)

1. Sepsis alert protocol activate in ED or ICU for severe sepsis/septic shock within 24 hours
2. Sensitivity analyses to account for possibility of over activation of sepsis protocol in the ED
3. Sepsis alert negative and identified independently by clinicians

The triage screening process is a composite “test” of multiple criteria. It would have been helpful to present the value of each of the criteria (e.g. how many more patients were identified by the inclusion of the criteria).

APPLICABILITY: The study population represents a single Children's hospital. Table 1 only includes age, gender and ED disposition. In particular, it would have been helpful to identify the proportion of patients with a high risk medical condition so that the study's results could be assessed for generalizability. In this ED that sees over 90,000 patients a year, sepsis was identified in less than 1 patient per day. It would be helpful to validate the process in a multicenter study including both children's hospital and community EDs.

Inter-rater reliability of the electronic triage process criteria and the clinical huddle was not reported. Some criteria are subjective. These include those that require clinical judgment such as the assessment of whether there are signs and symptoms of infection in the afebrile patient, whether the patient has an altered mental status and the thought process of the clinical huddle. In addition, the process for determining sepsis protocol activation from the bedside huddle is not clearly delineated. It would have been helpful to determine if there is a difference in accuracy between PEM faculty and fellows.

AUTHOR'S CONCLUSION: "In conclusion, we tested an electronic sepsis alert that uses a combination of vital signs, risk factors, and clinician judgment to identify children with severe sepsis in a large academic ED that manages more than 90,000 visits per year. This electronic sepsis alert improved recognition of severe sepsis, with a greater proportion of patients with sepsis being treated on the sepsis protocol. Sensitivity analyses for confounding by medical interventions do not suggest that the electronic sepsis alert resulted in overtreatment. Future efforts will focus on evaluating the ability to decrease unnecessary alerts while continuing to improve the sensitivity of the current system."

POTENTIAL IMPACT: An electronic sepsis alert tool when combined with clinical assessment had a "good" sensitivity and a high specificity for identifying severe sepsis. The sensitivity was improved by adding clinician assessment outside of the triage process highlighting the important of clinical judgement in the process. The proportion of missed sepsis patients decreased after implementation of the sepsis identification strategy. This single Children's hospital study's results may not be applicable to setting that encounters pediatric sepsis less frequently. Further validation of the process in a multicenter study including both children's hospital and community hospital EDs would be helpful.

APPENDIX: PEDIATRIC SEPTIC SHOCK DECISION ALGORITHM: AAP (WEB LINK)

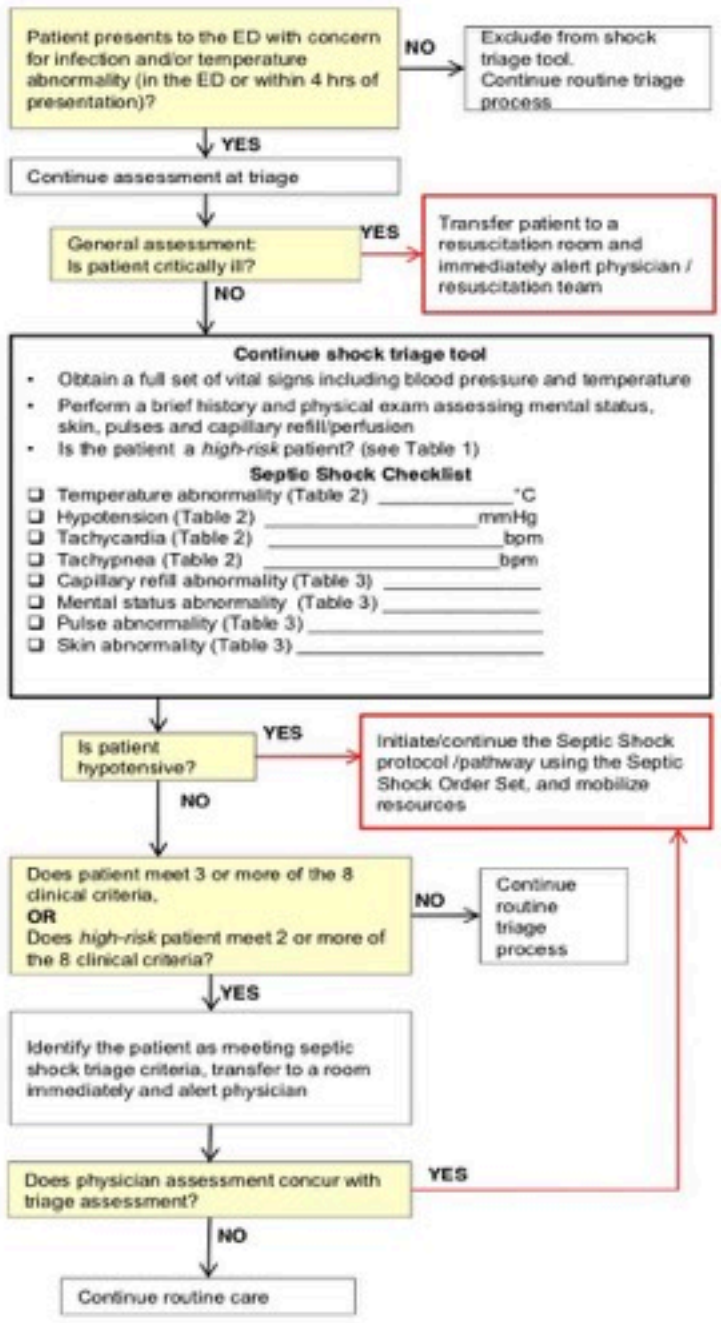

Table 1. High Risk Conditions

- Malignancy
- Asplenia (including SCD)
- Bone marrow transplant
- Central or indwelling line/catheter
- Solid organ transplant
- Severe MR/CP
- Immunodeficiency, immunocompromise or immunosuppression

Table 2. Vital Signs (PALS)

Age	Heart Rate	Resp Rate	Systolic BP	Temp (°C)
0 d – 1 m	> 205	> 60	< 60	<36 or >38
≥ 1 m - 3 m	> 205	> 60	< 70	<36 or >38
≥ 3 m - 1 r	> 190	> 60	< 70	<36 or >38.5
≥ 1 y - 2 y	> 190	> 40	< 70 + (age in yr × 2)	<36 or >38.5
≥ 2 y - 4 y	> 140	> 40	< 70 + (age in yr × 2)	<36 or >38.5
≥ 4 y - 6 y	> 140	> 34	< 70 + (age in yr × 2)	<36 or >38.5
≥6 y- 10 y	> 140	> 30	< 70 + (age in yr × 2)	<36 or >38.5
≥ 10 y - 13 y	> 100	> 30	< 90	<36 or >38.5
> 13 y	> 100	>16	< 90	<36 or >38.5

Table 3. Exam Abnormalities

	Cold Shock	Warm Shock	Non-specific
Pulses (central vs. peripheral)	Decreased or weak	Bounding	
Capillary refill (central vs. peripheral)	≥ 3 sec	Flash (< 1 sec)	
Skin	Mottled, cool	Flushed, ruddy, erythroderma (other than face)	Petechiae below the nipple, any purpura
Mental status			Decreased, irritability, confusion, inappropriate crying or drowsiness, poor interaction with parents, lethargy, diminished arousability, obtunded

STUDY: HIGH RISK CONDITIONS*
< 56 days**
Asplenia
Bone marrow or solid organ transplantation
Central line
Malignancy
Significant CNS/functional tech dependence
Immunodeficiency or Immunocompromised
*Based on AAP sepsis alert, **Study institution specific

SEPTIC SHOCK:
FLUID INFUSION TECHNIQUES

In children receiving non-emergent intravenous fluids, which method of fluid administration: pressure bag at 300 mmHg, a push pull system or gravity, adheres to the 2002 American College of Critical Care Medicines Guideline recommendations for administering 20 ml/kg of fluids within 5 minutes in the resuscitation of pediatric septic shock?

David Kessler M.D., Jeffrey Fine M.D.

December 2007

Stoner MJ, Goodman DG, Cohen DM, Fernandez SA, Hall MW.

RAPID FLUID RESUSCITATION IN PEDIATRICS: TESTING THE AMERICAN COLLEGE OF CRITICAL CARE MEDICINE GUIDELINE.

Ann Emerg Med. 2007 Nov;50(5):601-7.
PubMed ID: 17764783

STUDY DEFINITIONS	
POPULATION	Inclusion: Relatively healthy children (0-18 years) receiving a non-emergent isotonic intravenous fluid bolus through a previously placed antecubital intravenous catheter. Exclusion: No functional antecubital vein catheter, any bolus isotonic intravenous fluids during the same ED visit, hypotension, in arrest, at high risk for complications caused by rapid fluid administration (history of unrepaired congenital heart disease; a diagnosis of cardiomyopathy, myocarditis, or chronic arrhythmia; a gallop rhythm, bilateral crackles, or hepatomegaly on physical examination), medications (digoxin, furosemide, spironolactone, or an angiotensin-converting enzyme inhibitor), sickle cell disease. Setting: Single, Children's Hospital ED, 9/2005-4/2006
INTERVENTION	Pressure Bag Group: Inflatable sleeve pumped up to a pressure of 300 mm Hg. Pressure maintained by periodically re-pressurizing the bag Push-Pull Group: Sterile 3-way stopcock interposed between the blood tubing and T-connector. A sterile 30 ml (<1 year) or 60 mL (≥ 1 year) syringe placed on the stopcock. Alternately pull from the isotonic intravenous fluid bag, turn the stopcock, and then push to the patient as fast as possible.
CONTROL	Gravity Group: Tubing clamped in the "wide open" position
CO-INTERVENTIONS	1,000-mL bag of sterile normal saline through a standard straight-type blood infusion set and a standard-bore T-connector hung from a digital suspension scale at a height of 0.9 meters (3 feet) above chest level. If infiltration occurred subject participation was concluded
OUTCOMES	1. Volume of fluid administered (ml/kg) during the study period (5 minutes) 2. Absolute rate of fluid delivery (ml/kg/minute) 3. Proportion achieving ACCM recommendation of 20 mL/kg within 5 minutes.
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Block randomization was done in blocks of 3,6 & 9
Was randomization concealed?	Yes. Numbered opaque envelopes were used.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Only one patient (in the push/pull group) was unable to continue due to infiltrated intravenous catheter. This patient was included in an intention to treat analysis. 3 other patients were excluded (one from each group) for protocol violations (using a different sized T-connector). These 3 patients were not included in the ITT analysis.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Patients, parents, physicians and research staff were not blinded to treatment group.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Data was available for 100% (60/60) of patients.
Were patients analyzed in the groups to which they were randomized?	Yes. 95% (57/60) of patients were included in the primary intention to treat analysis.
Was the trial stopped early?	No. The trial was not stopped early.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 57 (3 excluded for protocol violations)
Push-Pull: 1/19 intravenous infiltrate, included in ITT analysis

PRIMARY OUTCOMES:
1. Fluid volume (ml/kg) delivered in 5 min
2. Rate of fluid administration (ml/kg/min)
3. Proportion receiving 20ml/kg in 5 min

	GRAVITY	PUSH/PULL	PRESSURE
1. ml/kg in 5 min	6.2 (5.2-7.3)*	20.9 (16.6-22.2)	20.2 (14.8-22.2)
2. ml/kg/min	1.2 (1.0-1.5)	4.4 (2.4-5.9)	4.6 (3.3-5.4)
3. ≥ 20ml/kg in 5 minutes	0%	68%	58%
* Median (IQR)			

No statistical significant difference between Push/Pull and Pressure groups for any of the 3 outcomes.

Subgroup Analysis:
No one > 40 kg achieved 20 ml/kg in 5 minute

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence Intervals were not presented. Precision expressed as an interquartile range around the median. See table above.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	No. Limited demographic data were presented. It is unclear what the indications for a fluid bolus were in these non-emergent patients. While measurements were made in vivo, these were not septic patients. It is unclear from this study if septic patients will experience higher rates of adherence or complications with one of the methods.
Were all patient important outcomes considered?	No. It may have been useful to record intravenous catheter failure rates occurring beyond 5 minutes. It is also unclear that these 5 minute rates can be sustained over 15 minutes with repeated fluid boluses.
Are the likely treatment benefits worth the potential harm and costs?	Possibly. This study does not attempt to address the efficacy of the ACCM guidelines in pediatric resuscitation, but merely assigns fluid volume administration rate as a proxy for successful resuscitation. From that standpoint, it demonstrates two feasible methods for rapid fluid infusion with no clinically significant adverse events (though the study is not powered to identify rare adverse outcomes).

CLINICAL BOTTOM LINE

BACKGROUND: The American College of Critical Care Medicine (ACCMP) published guidelines in 2002 which recommend 20 ml/kg boluses of isotonic intravenous fluids up to 60 ml/kg within the first 15 minutes of resuscitation if shock persists. These recommendations were based on a study that demonstrated that children in septic shock receiving 60 ml/kg in the first hour had lower mortality without an increase in adverse events (Carcillo, JAMA 1991, PubMed ID: 1870250). These goals are often thought to not be technically feasible due to the small caliber of angiocatheters used in children.

CLINICAL QUESTION: In children receiving non-emergent intravenous fluids, which method of fluid administration: pressure bag at 300 mmHg, a push pull system or gravity, adheres to the 2002 American College of Critical Care Medicines Guideline recommendations for administering 20 ml/kg of fluids within 5 minutes in the resuscitation of pediatric septic shock?

DESIGN/VALIDITY: This was a randomized clinical that included 57 patients in the primary intention to treat analysis. The trial was well designed but suffered from using a well child model for pediatric septic shock. In is unclear that the fluid rates achieved would be the same in the hypotensive patient. In addition, two study personnel served as operators for the push-pull group. This may overestimate the efficacy of this method. The physicians and patients were not blinded to the study group though this is unlikely to affect the assessment of objective outcome measures.

PRIMARY RESULTS: The study demonstrated that the pressure bag (58%) and push pull (68%) methods were clearly better at achieving the desired fluid volume when compared to the gravity group (0%). Even though these were more successful they did not achieve a 70% compliance with the ACCM Guidelines. The pressure bag and push pull methods are labor intensive and required dedicated staff to complete. Operator fatigue may contribute to the low adherence rate seen. In a subgroup analysis, no patients over 40 kg achieved the desired fluid volume in either study group despite larger catheters.

APPLICABILITY: It is unclear if the results of this study can be generalized to pediatric septic shock patients. In addition, this study only collected data over 5 minutes and the results may not be generalizable to the recommendation of administering 60ml/kg over 15 minutes.

AUTHOR'S CONCLUSION: "Our findings suggest that the ACCM guideline of 5 minutes for the administration of 20 mL/kg of resuscitative fluids is feasible. Although it was only the minority of subjects in the pressure bag and push-pull groups that failed to meet this guideline, it is likely that the majority of those subjects would have completed a 20 mL/kg infusion within 10 minutes, suggesting that rapid fluid administration is indeed possible in large and small children. The use of a properly inflated pressure bag and the use of a manual push-pull system both appear to be acceptable methods of rapid fluid delivery in children. Furthermore, our data indicate that the administration of bolus fluid by gravity likely has a limited role in the acute management of pediatric septic shock. Although traditional intravenous pumps and rapid infuser devices may be practical for use with a small percentage of children with septic shock, it is important for practitioners to understand that there are inexpensive, readily available alternatives that permit ACCM guideline adherence."

POTENTIAL IMPACT: Additional work needs to be done to determine the optimal method for rapid fluid resuscitation in the pediatric patient with shock. The pressure bag and push-pull methods may offer a better alternative to the gravity method in the patient less than 40 kg but require dedicated staff.

SEPTIC SHOCK:
FLUID RESUSCITATION (AFRICA)

In African children between 60 days and 12 years of age with severe febrile illness and impaired perfusion, does rapid and early fluid resuscitation with either a saline bolus or a 5% albumin bolus reduce mortality when compared to no fluid bolus?

Janienne Kondrich, M.D., Karen Goodman, M.D.
June 2011

Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, Nyeko R, Mtove G, Reyburn H, Lang T, Brent B, Evans JA, Tibenderana JK, Crawley J, Russell EC, Levin M, Babiker AG, Gibb DM
FEAST Trial Group.

MORTALITY AFTER FLUID BOLUS
IN AFRICAN CHILDREN WITH SEVERE INFECTION

N Engl J Med. 2011 Jun 30;364(26):2483-95.
PubMed: 21615299

STUDY DEFINITIONS	
POPULATION	Inclusion: 60 days -12 years, severe febrile illness complicated by impaired consciousness (prostration or coma), respiratory distress (increased work of breathing), or both, and with impaired perfusion (capillary refill time ≥ 3 seconds, lower-limb temperature gradient, weak radial-pulse volume, or severe tachycardia (>180 beats per minute in children younger than 12 months of age, >160 beats per minute in children 1 to 5 years of age, or >140 beats per minute in children older than 5 years of age)). Those with severe hypotension (< 50 mmHg < 1 year, < 60 mm 1-5 years, < 70 mm Hg < 5 years) were analyzed separately. Exclusion: Severe malnutrition, gastroenteritis, noninfectious causes of shock (e.g., trauma, surgery, or burns), volume expansion contraindicated. Setting: 6 clinical centers: Kenya (1), Tanzania (1), Uganda (4), 1/2009-1/2011
INTERVENTION	Normal saline 20 ml/kg over 1 hour, repeat if remain with poor perfusion at 1 hour, given 40 ml/kg if developed severe hypotension
	Albumin (5%) 20 ml/kg over 1 hour, repeat if remain with poor perfusion at 1 hour, given 40 ml/kg if developed severe hypotension
CONTROL	No fluid bolus. 40 ml/kg of normal saline if develop severe hypotension (< 50 mmHg < 1 year, < 60 mm 1-5 years, < 70 mm Hg < 5 years)
OUTCOME	Primary Outcome: Mortality at 48 hours after randomization. Secondary Outcomes: Mortality at 4 weeks Neurologic sequelae at 4 and 24 weeks Hypotensive shock within 48 hours Adverse events related to fluid resuscitation: pulmonary edema, increased intracranial pressure, and severe allergic reaction.
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized in permuted blocks of random sizes. Randomization was stratified by clinical center.
Was randomization concealed?	Yes. The group assignments were kept inside opaque, sealed envelopes which were numbered consecutively and opened in numerical order by a study clinician.
Were patients in the study groups similar with respect to known prognostic factors?	All three groups were similar on most measured characteristics. Prostration (defined as the inability of a child older than 8 months of age to sit upright or the inability of a child 8 months of age or younger to breastfeed) and coma (inability to localize a painful stimulus) were slightly less in the no bolus group. Although the percentage of patients with hemoglobin < 5 gm/dL was provided, sickle cell disease status of the patients was not.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	A committee who reviewed all deaths, neurologic sequelae, and adverse events were blinded to the treatment assignments. It was not explicitly stated, but it does not appear that the any of the treating study clinicians were blinded.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Follow-up for the primary outcome (mortality at 48 hours) was near complete. A total of 17 patients (0.7%, 0.8%, and 0.2% for the Albumin, Saline and Control groups, respectively), were lost to follow up at 48 hours. These patients either withdrew from the study or were taken from the hospital prior to 48 hours. An additional 70 patients (2.2%) were lost to follow-up at 28 days.
Were patients analyzed in the groups to which they were randomized?	All analyses were performed per the intention to treat principle.
Was the trial stopped early?	Yes. An independent data and safety monitoring committee recommended stopping enrollment in January 2011 after 3,141 of the planned 3,600 patients were enrolled. This decision was due to both safety concerns in the saline and albumin bolus groups and because it was unlikely that superiority of the bolus group over the control group would be demonstrated.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Primary Outcome**:** Mortality at 48 hours:
Saline bolus group: 110/1,047 (10.5%)
Albumin bolus group: 111/1,050 (10.6%)
No bolus group: 76/1,044 (7.3%)

Saline v No Bolus
Risk Difference: 10.5%–7.3% = 3.2%, 95% CI (0.8, 5.7%)
Relative Risk: 10.5/7.3 = 1.44, 95% CI (1.09, 1.90)

Albumin v No Bolus
Risk Difference: 10.6% - 7.3% = 3.3%, 95% CI (0.8, 5.8%)
Relative Risk: 10.6/7.3 = 1.45, 95% CI (1.10, 1.92)

Bolus (Albumin + Saline groups) vs. No bolus:
Risk difference: 10.5%– 7.3% = 3.3%, 95% CI (1.2, 5.3%)
Relative risk: 10.54%/7.27% = 1.45, 95% CI (1.13, 1.86)

Subgroup Analysis
The difference remained significant when subgroups of +/- malaria, +/- Hemoglobin < 5 gm/dl and +/- lactate > 5 millimol/liter were analyzed (see Figure 3)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See confidence intervals provided above. The confidence interval for both the absolute risk difference and relative risk are statistically significant. There was a statistically significant lower mortality at 48 hours in the no bolus group compared to each of the bolus group individually and combined. In their power analysis, the authors defined as clinically significant an absolute risk difference of 22% for Saline compared to Control and 29% for Albumin compared to Control. The study difference was 3.3%

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	No. All study patients were enrolled in Uganda, Kenya and Tanzania, and had more severe illness than the patient population we see in the United States due to the lack of standardized immunizations programs, malnutrition, poverty and poor health care infrastructure.
Were all patient important outcomes considered?	Yes. The outcomes considered at both 48 hours (death, episodes of hypotensive shock, adverse events potentially related to fluid resuscitation) and 28 days (death, neurologic sequelae) were comprehensive.
Are the likely treatment benefits worth the potential harm and costs?	This study did not demonstrate any treatment benefit and had at statistically significant increased mortality in the bolus therapy groups.

CLINICAL BOTTOM LINE

BACKGROUND: The standard of care for patients with septic shock in the United States is rapid, early fluid resuscitation, as delineated in both the AHA/Pediatric Advanced Life Support and American College of Critical Care Medicine guidelines. The World Health Organization guidelines, suggest that fluid resuscitation is to be reserved for patients with advance shock. This study sought to demonstrate the benefit of early fluid resuscitation therapy with either a saline or 5% albumin bolus in African children who presented, essentially, in septic shock – with severe, febrile illness and evidence of impaired perfusion but without severe hypotension (hypotension (< 50 mmHg < 1 year, < 60 mm 1-5 years, < 70 mm Hg < 5 years).

CLINICAL QUESTION: In African children between 60 days and 12 years of age with severe febrile illness and impaired perfusion, does rapid and early fluid resuscitation with either a saline bolus or a 5% albumin bolus reduce mortality when compared to no fluid bolus?

DESIGN/VALIDITY: This was a well-designed multicenter, randomized clinical trial with a significant sample size and an unexpected outcome. The study included 3,141 patients in the primary analysis. A subgroup of 29 patients with severe hypotension was also included but not discussed in this review due to the small sample size.

PRIMARY RESULTS: Mortality at 48 hours was statistically significant less in the control group when analyzed against each fluid bolus group individually and when combined (Absolute risk difference: Saline + Albumin groups – Control group = 10.54% – 7.27% = 3.3% (1.2, 5.3). In their power analysis, the authors defined as clinically significant an absolute risk difference of 22% for Saline compared to Control and 29% for Albumin compared to Control.

The reason for this decreased which contradicts current guidelines is unclear. It does not appear to be due to potential adverse effects of aggressive fluid resuscitation such as pulmonary edema or increased intracranial pressure, as these occurred clinically in only a few children.

APPLICABILITY: The patients in this study differed greatly from most patients seen in the emergency departments in the United States, in level of illness severity, time of presentation to medical care, nutrition status, among other determinants. Nearly a third had visible jaundice, 57% were positive for malaria and the mean hemoglobin was 7.1 gm/dl. However, the difference in mortality at 48 hours remained significantly greater for the fluid bolus study groups when subgroups with/without: malaria, hemoglobin < 5 gm/dl and lactate > 5 mmol/liter were analyzed. It may have been informative to know whether sickle cell disease status differed between the treatment groups.

AUTHOR'S CONCLUSION: "In conclusion, the results of this study challenge the importance of bolus resuscitation as a lifesaving intervention in resource-limited settings for children with shock who do not have hypotension and raise questions regarding fluid-resuscitation guidelines in other settings as well."

POTENTIAL IMPACT: This study raises questions as to whether our current guidelines for fluid resuscitation can result in harm for our more critically ill patients and requires further study in other settings.

The 2015 update of American Heart Association Pediatric Advanced Life Support Course included the follow recommendation: “Administration of an initial fluid bolus of 20 mL/kg to infants and children with shock is reasonable, including those with conditions such as severe sepsis, severe malaria and Dengue. When caring for children with severe febrile illness in settings with limited access to critical care resources (i.e., mechanical ventilation and inotropic support), administration of bolus intravenous fluids should be undertaken with extreme caution because it may be harmful. Providers should reassess the patient after every fluid bolus.”

SEPTIC SHOCK:
FLUID RESUSCITATION RATE

In pediatric patients with fluid refractory septic shock, is a higher rate of fluid administration within the first hour associated with an increase in survival without an accompanying increase in non-cardiogenic pulmonary edema (acute respiratory distress syndrome) or cardiogenic pulmonary edema?

Michael Mojica, M.D.
June 2017

Carcillo JA, Davis AL, Zaritsky A.

ROLE OF EARLY FLUID RESUSCITATION IN PEDIATRIC SEPTIC SHOCK

JAMA. 1991 Sep 4;266(9):1242-5.
PubMed ID: 1870250

STUDY DEFINITIONS	
POPULATION	Inclusion: Children presenting to the ED in septic shock with a pulmonary artery catheter at 6 hours after presentation Sepsis: (+) Blood culture, pathologic organism from a tissue site (on autopsy), included 1 patient with HSV and 1 patient with disseminated candidiasis. Shock: Blood pressure < 2 standard deviation for age with 3 of 4 of the 1. Decreased peripheral pulses 2. Mottle or cool extremities 3. Tachycardia: > 180 beats/min if < 5 years, > 160 beats/min if ≥ 5 years 4. Urine output < 1 ml/kg/hour if ≤ 20 kg, < 20 ml/hour if > 20 kg Exclusion: Uncorrected congenital heart disease with R to L or L to R shunts due to unreliability of cardiac outputs with pulmonary artery catheters Setting: Single Children's Hospital Emergency Department, 1982-89
EXPOSURE	Group 1: < 20 ml/kg of fluid* in the first hour Group 2: 20-40 ml/kg of fluid* in the first hour
CONTROL	Group 3: > 40 ml/kg of fluid* in the first hour
CO-INTERVENTIONS	*Fluid could be crystalloid (Normal saline or Ringer's lactate) or colloid (5% albumen, packed RBCs, fresh frozen plasma, cryoprecipitate) No specific protocol for fluid resuscitation existed Pulmonary artery catheter placed for shock refractory to fluid resuscitation All patients received vasopressor or inotropic support. Therapeutic decisions by ED and PICU caregivers
OUTCOMES	Primary Outcome: Survival to hospital discharge Secondary Outcomes: Non-cardiogenic pulmonary edema (ARDS) within the 1st 24 hours: 1. Alveolar infiltrated on chest XRAY 2. PaO2 < 60 mmHg in room air 3. Pulmonary capillary wedge pressure ≤ 15 mgHg Cardiogenic pulmonary edema within in the 1st 24 hours 1. Alveolar infiltrated on chest XRAY 2. PaO2 < 60 mmHg in room air 3. Pulmonary capillary wedge pressure > 15 mgHg Hypovolemia at 6 hours 1. Urine output < 1 ml/kg/hour if ≤ 20 kg, < 20 ml/hour if < 20 kg, 2. Blood pressure < 2 SD below mean for age 3. Pulmonary capillary wedge pressure ≤ 8 mmHg
DESIGN	Observational: Retrospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
ASIDE FROM THE EXPOSURE OF INTEREST DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or did statistical adjustments address the imbalance).	Yes. See Table 1. Patients were similar regarding age, proportion with chronic vs acute illness and proportion with gram positive vs gram negative organisms. Many factors that could influence the outcome of survival were not included in Table 1. These include; initial vital signs, the timing and appropriateness of antimicrobials administered, the type and dosage of vasoactive agents required and whether source control was required.
Were the circumstances and methods for detecting the outcome similar?	Yes. Patients were identified and charts were reviewed following initial therapy. Age, weight, diagnosis, vital signs and hemodynamic monitoring were recorded for the first 24 hours.
Was follow-up sufficiently complete?	Unclear. Patients were followed to hospital discharge. The mechanism for follow up after discharge is not presented though the 1 death that occurred in group 3 was described as a 2nd episode of sepsis two weeks later.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

N = 34 with culture or tissue positive septic shock
Mortality: 47% (16/34)
Median age: 13.5 months
Preexisting condition: 31% (11/34)
Required mechanical ventilation: 82% (28/34)

FLUIDS RECEIVED IN 1ST HOUR

	Mean ± SD
Group 1: < 20 ml/kg	11 ± 6 ml
Group 2: 20-40 ml/kg	32 ± 5 ml
Group 3: > 40 ml/kg	69 ± 19 ml
Survivors	42 ± 28 ml
Non-survivors	23 ± 18 ml
All	33 ± 36 ml

SEE RESULTS TABLE IN THE CLINICAL BOTTOM LINE

Survival in Group 3 was statistically significant greater than Group 1 and Group 2 individually and combined

Persistent hypovolemia was statistically significantly lower in Group 3 compared to Group 1 but not for Group 3 compared to Group 2 or compared to Group 1 and Group 2 combined.

All patients with persistent hypovolemia at 6 hours died

There was no statistically significant difference between the 3 groups for the development of acute respiratory distress syndrome or cardiogenic pulmonary edema within 24 hours

HOW PRECISE IS THE ESTIMATE OF THE RISK?

Risk differences or relative risks with confidence intervals were not provided for the group comparisons.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Possibly. This was a small sample of patients from a single pediatric emergency department. Only age, gender, and the presence of absence of an underlying medical condition were presented.
Was follow-up sufficiently long?	The mechanism for follow up after discharge is not presented though the 1 death that occurred in group 3 was described as a 2nd episode of sepsis two weeks later.
Is the exposure similar to what might occur in my patient?	Possibly. It is very unlikely, given current recommendations, that a patient in fluid refractory septic shock will receive less than 20 ml/kg in the first hour. In addition, they would likely only receive < 40 ml/kg if they responded to an initial fluid bolus with normal hemodynamic parameters.
What is the magnitude of the risk?	Survival in Group 3 (88.9%) was statistically significant greater than group 1 (42.9%) and group 2 (36.4%) individually and combined (40%). This difference is large and clinically significant as well.
Are there any benefits that offset the risks associated with exposure?	No. The use of smaller volumes of resuscitation fluids was not associated with a lower risk of acute respiratory distress syndrome or cardiogenic pulmonary edema.

CLINICAL BOTTOM LINE

BACKGROUND: Septic shock is a form of distributive shock. Septic shock includes elements of hypovolemic shock. A relative hypovolemia occurs due to vasodilation and fluids are lost to the extravascular space due capillary leakage. In addition, septic shock has elements of cardiogenic shock and fluid resuscitation can increased preload leading to an increase in cardiac output due to an increase I stroke volume. The optimal rate of fluid administration for pediatric patients in septic shock is unknown. Children are thought to better tolerate fluid boluses but the adverse effects of multiple fluid boluses are also unknown.

CLINICAL QUESTION: In pediatric patients with fluid refractory septic shock is a higher rate of fluid administration within the first hour associated with an increase in survival without an accompanying increase in non-cardiogenic pulmonary edema (acute respiratory distress syndrome) and cardiogenic pulmonary edema?

DESIGN/RISK OF BIAS: This was a retrospective cohort of pediatric patients with septic shock. In current terminology, the patients in this study would be considered to have fluid refractory septic shock and most would likely meet criteria for catecholamine resistant shock as well. The study included 34 patients in the primary analysis. 47% of the patients died.

The study analyzed the association of the amount of fluids administered in the first hour of resuscitation to determine the impact on survival and persistent hypovolemia at 6 hours and adverse effects of fluid administration such as non-cardiac pulmonary edema (adult respiratory distress syndrome) and cardiogenic pulmonary edema.

3 groups of patients were analyzed based on the amount of fluids received within 1 hour (Group 1 received < 20 ml/kg, group 2 received 20-40 ml/kg and group 3 received > 40 ml/kg). No specific protocol for fluid resuscitation was provided. In addition, a variety of fluids was administered. Fluid could be crystalloid (Normal saline or Ringers lactate) or colloid (5% albumen, packed RBCs, fresh frozen plasma, cryoprecipitate).

Patients were similar regarding age, proportion with chronic vs acute illness and proportion with gram positive vs gram negative organisms. Many factors that could influence the outcome of survival were not included presented. These include; initial vital signs, the timing and appropriateness of antimicrobials administered, the type and dosage of vasoactive agents required and whether source control was required. A regression analysis including these factors would have been helpful to delineate the independent effects of the amount of fluids administered in the first hour on the study's outcomes.

The study is susceptible is biases inherent to retrospective cohort studies. As the authors acknowledge in the discussion, statistically significant comparisons represent an association and not causality.

PRIMARY OUTCOME: Survival in Group 3 (88.9%) was statistically significant greater than group 1 (42.9%) and group 2 (36.4%) when analyzed individually and when group 1 and group 2 were combined (40%). Persistent hypovolemia was statistically significantly lower in group 3 (0%) compared to group 1 (42.9%) but not when group 3 was compared to group 2 (18.2%) or when group 3 was compared to group 1 and group 2 combined (32%). All 8 patients with persistent hypovolemia at 6 hours died.

There were no adverse events associated with initially higher volume of fluid resuscitation. There was no statistically significant difference between the groups for the development of non-cardiogenic pulmonary edema (acute respiratory distress syndrome) or cardiogenic pulmonary edema.

		Survivors[1]	Persistent Hypovolemia at 6 hours[3]	ARDS With 24 hours[4]	Cardiogenic Pulmonary Edema with 24 hours[4]
		Figure 1	Table 3	Table 4	Table 4
1	< 20 ml/kg	6/14 (42.9%)	6/14 (42.9%)	6/14 (42.9%)	2/14 (14.3%)
2	20-40 ml/kg	4/11 (36.4%)	2/11 (18.2%)	8/11 (72.7%)	2/11 (18.2%)
3	> 40 ml/kg	8/9 (88.9%)[2]	0/9 (0%)	4/9 (44.4%)	3/9 (33.3%)

1. Survival in Group 3 was statistically significant greater than survival in Group 1 and Group 2 individually and when Group 1 and 2 are combined
2. The single patient death in group 3 occurred 2 weeks later from a second episode of sepsis
3. Persistent hypovolemia was statistically significantly lower in Group 3 compared to Group 1 but not for Group 3 compared to Group 2 or compared to Group 1 and Group 2 combined.
4. No statistically significant difference between the 3 groups for either adverse outcome.

APPLICABILITY: The study's conclusions are based on a small sample size (n=34) at a single institution with fluid refractory septic shock and at least ½ with catecholamine resistant shock. The mean age of patients was 13.5 months possibly limited generalizability to older children and adolescents.

AUTHOR'S CONCLUSION: "Based on our findings, repeated 20-ml/kg fluid boluses may be administered in excess of 60 ml/kg in the first hour, and 120 ml/kg in the first 6 hours if blood pressure, peripheral pulses, mental status, arterial blood gas levels, urine output and peripheral color suggests that perfusion remains decreased. Large volumes of isotonic fluid can be administered, when clinically indicated, without significantly increasing the risk of pulmonary edema or the syndrome of inappropriate antidiuretic hormone secretion. Regardless of the total fluid volume administered, intravascular monitoring in the form of pulmonary artery catheters or central venous catheters may be necessary to reliably diagnose persistent hypovolemia, non-cardiogenic pulmonary edema and cardiogenic pulmonary edema during subsequent resuscitation. Placement of these intravascular catheters should not delay early fluid administration however.

POTENTIAL IMPACT: It is fascinating to re-read this study from a critical appraisal viewpoint after quoting its conclusions for over 20 years. It is essential to remember that this is an observational design with a small sample size. The authors emphasize and that an association does not necessarily represent a causal relationship.

A more recent study conducted in recourse poor settings (Maitland, NEJM 2011, PubMed: 21615299) demonstrated that mortality at 48 hours was statistically significant less in the group not receiving fluid boluses when analyzed against each fluid bolus group individually and when combined (Absolute risk difference: 3.3% (1.2, 5.3). The authors conclude: "the results of this study challenge the importance of bolus resuscitation as a lifesaving intervention in resource-limited settings for children with shock who do not have hypotension and raise questions regarding fluid-resuscitation guidelines in other settings as well."

The 2015 update of American Heart Association Pediatric Advanced Life Support Course included the following recommendation: “Administration of an initial fluid bolus of 20 mL/kg to infants and children with shock is reasonable, including those with conditions such as severe sepsis, severe malaria and Dengue. When caring for children with severe febrile illness in settings with limited access to critical care resources (i.e., mechanical ventilation and inotropic support), administration of bolus intravenous fluids should be undertaken with extreme caution because it may be harmful. Providers should reassess the patient after every fluid bolus.”

The 2017 American College of Critical Care Medicine provide the following recommendation for fluid resuscitation in septic shock based on Level IC evidence. “Rapid fluid boluses of 20 mL/kg (isotonic crystalloid or 5% albumin) can be administered by push or rapid infusion device (pressure bag) while observing for signs of fluid overload (i.e., the development of increased work of breathing, rales, cardiac gallop rhythm, or hepatomegaly). In the absence of these clinical findings, children can require 40–60 mL/kg in the first hour. Fluid can be pushed with the goal of attaining normal perfusion and blood pressure. Hypoglycemia and hypocalcemia should be corrected. A 10% dextrose containing isotonic IV solution can be run at maintenance IV fluid rates to provide age appropriate glucose delivery and to prevent hypoglycemia.” (Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock, Critical Care Medicine 2017, PubMed ID: 28509730).

SEPTIC SHOCK:
LACTATE AND ORGAN DYSFUNCTION

In pediatric patients (1-19 years) with systemic inflammatory response syndrome (temperature and heart rate criteria only) does an elevated lactate level > 4 mmol/L accurately predict subsequent organ dysfunction at 24 hours?

Maria Lame M.D., Karen Goodman M.D.
January 2013

Scott HF, Donoghue AJ, Gaieski DF, Marchese RF, Mistry RD.

THE UTILITY OF EARLY LACTATE TESTING
IN UNDIFFERENTIATED PEDIATRIC
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

Acad Emerg Med. 2012 Nov;19(11):1276-80.
PubMed ID: 23167859

STUDY DEFINITIONS	
POPULATION	Inclusion: < 19 years, met pediatric SIRS criteria (temperature of > 38.5 or < 36° C and a heart rate greater than two standard deviations (SDs) above normal for age), underwent phlebotomy or central venous catheter access Exclusion: Transferred from another facility, history of an inborn errors of metabolism, lactate not measured within 15 minutes of intravenous therapy Setting: Single Children's hospital ED, Enrollment period not presented.
DIAGNOSTIC TEST	Point of care venous lactate without restriction on tourniquet use Hyperlactatemia defined as Lactate ≥ 4 mmol/liter
REFERENCE STANDARD	Organ dysfunction within 24 hours of triage time (See Appendix) International Pediatric Sepsis Consensus Conference definitions
OUTCOME	Test characteristics of point of care venous lactate ≥ 4 mmol/liter Area under the receiver operating characteristic curve
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. The patients presented meeting criteria for SIRS. It is difficult to confidently predict which patient may have a benign course from those that may progress to sepsis or severe sepsis. The prevalence of organ dysfunction in this sample was 5.4%. Lactate level was drawn where clinical judgment already deemed these children to be systemically ill and risk stratification occurred, creating the possibility of selection bias.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The investigators used organ dysfunction as classified by the International Pediatric Sepsis Consensus Conference definitions which were modified by the exclusion of serum lactate as a criterion.
Were those interpreting the test and reference standard blind to the other results?	No. Clinical providers were blinded to lactate levels. Patients were enrolled by research assistants, who collected lactate levels. The outcome was determined by unblinded review of medical records.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	Unclear. The reference standard was organ dysfunction as indicated by an adapted version of the International Pediatric Sepsis Consensus Conference definitions. It is not clear if all patients received each of the laboratory tests required to meet criteria.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

	24-HOUR ORGAN DYSFUNCTION		
	YES	NO	
LACTATE ≥ 4	4	14	18
LACTATE < 4	9	212	221
	13	226	239

Prevalence: 13/239 = 5.4%
Sensitivity: 4/13 = 31%, 95%, CI (13, 58%)
Specificity: 212/226 = 94%, 95% CI (90, 96%)
Predictive Value (+) Test: 4/18 = 22%, 95% CI (9, 45%)
Predictive Value (-) Test**:** 212/221 = 96%, 95% CI (92, 98%)

In the study population with a pretest probability of organ dysfunction of 5.4% the lactate level stratified patients into a high-risk group with a 22% post-test probability and a low-risk group with a 4% post-test probability of organ dysfunction

Relative Risk (Lactate ≥4/Lactate <4)
= (4/18)/(9/221) = 5.5, 95%CI (1.9-16)

Likelihood Ratios
Likelihood Ratio (+) Test: (4/13)/(14/226) = 5.16, 95% CI (1.9 – 13.0)
Likelihood Ratio (-) Test: (9/13)/(212/226) = 0.73, 95% CI (0.5 – 1.0)

Lactate Accuracy as a Continuous Test:
Area under the receiver operating characteristic curve (AUC) = 0.62, 95% CI (0.45 to 0.89)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Yes. Lactate levels are objective and not open to interpretation. The reproducibility of serum lactate depends on the precision of the assay used.
Are the study results applicable to the patients in my practice?	Unclear. The authors failed to provide demographic information. The only information provided with is that patients were 19 and younger who presented to a tertiary care children hospital that met two SIRS criteria.
Will the test results change my management strategy?	No, a single lactate measurement cannot confidently exclude or confirm serious illness. The low sensitivity prevents the use of lactate to rule out serious illness. The specificity is not high enough to be used as an independent tool to rule in. Clinical judgment will continue to play major role in risk stratification.
Will patients be better off as a result of the test?	As a single test lactate cannot be used to reliably rule in or rule out disease. It may be helpful in conjunction with other clinical and laboratory parameters.

CLINICAL BOTTOM LINE

BACKGROUND: Children presenting with systemic inflammatory response syndrome, can potentially rapidly progress to severe sepsis and septic shock. In adults, an early, elevated lactate predicts mortality. Early recognition is the key to initiating goal directed therapy. Currently, there are no defined standard laboratory criteria to help identify children at risk for subsequent organ dysfunction.

CLINICAL QUESTION: In pediatric patients (1-19 years) with systemic inflammatory response syndrome (temperature and heart rate criteria only) does an elevated lactate level >4 mmol/L accurately predict subsequent organ dysfunction at 24 hours?

DESIGN/RISK OF BIAS: In this single-center, prospective, observational cohort study, the authors attempt to ascertain whether an ED serum lactate of greater 4.0 mmol/L predicts organ dysfunction within 24 hours of triage in pediatric patients presenting with SIRS. The analysis included 239 patients of which 5.4% had organ failure.

PRIMARY RESULTS: The low sensitivity (31%) prevents the use of lactate to rule out serious illness and the specificity (94%) is not high enough to be used as an independent test to rule it in. In the study population with a pretest probability of organ dysfunction of 5.4% the lactate level stratified patients into a high-risk group with a 22% post-test probability and a low-risk group with a 4% post-test probability of organ dysfunction. The area under the receiver operating characteristic curve of 0.623 (CI 95% .445 to . 89), demonstrating a limited ability to discriminate between those with and without organ dysfunction based on lactate level.

APPLICABILITY: The authors fail to provide an adequate description of the study population limiting generalizability and the population if from a single center.

AUTHOR'S CONCLUSION: "The ability to distinguish a child with an innocent febrile illness from one with impending sepsis with organ dysfunction remains a vital consideration for acute care providers for children. We found that serum lactate measurement identifies a population at higher risk for severe outcomes than the broader pediatric ED population with fever and tachycardia and would be a useful addition to clinical assessment in pediatric sepsis clinical and research protocols."

POTENTIAL IMPACT: The study demonstrates and that a single lactate measurement cannot reliably exclude or confirm subsequent organ dysfunction. Serum lactate may provide valuable information about a patient's physiological status in the context of other clinical signs and symptoms. Interestingly, Clinical judgment identified most children that developed organ dysfunction, demonstrated by decreased time to therapy in children that developed organ dysfunction.

APPENDIX: STUDY CRITERION STANDARD

STUDY ORGAN DYSFUNCTION DEFINITIONS*
CARDIOVASCULAR DYSFUNCTION: (any of the following): Despite isotonic IV bolus ≥ 40 mL/kg • Systolic blood pressure < 5% for age • Need for vasoactive drug: dopamine >5 mcg/kg/min or dobutamine, epinephrine, norepinephrine • Capillary refill > 5 seconds • Urine output < 0.5 ml/kg/hour
RESPIRATORY DYSFUNCTION: (any of the following) • PaO_2/FIO_2 < 300 in absence of cyanotic heart disease or preexisting lung disease • $PaCO_2$ > 65 torr or 20 mm Hg over baseline • Proven need for > 50% FIO_2 to maintain saturation ≥ 92%
NEUROLOGIC DYSFUNCTION: (any of the following) • Glasgow Coma Scale ≤ 11 or acute change ≥ 3 points below abnormal baseline
HEMATOLOGIC DYSFUNCTION: (any of the following): • Platelets < 80,000 or decline of 50% from highest value over past three days in patients with baseline low platelets • International normalized ratio > 2
RENAL DYSFUNCTION: • Creatinine ≥ 2 times upper limit for age or twofold increase in baseline creatinine in patients with baseline elevations in creatinine
HEPATIC DYSFUNCTION (any of the following): • Total bilirubin ≥ 4 (not applicable to newborn) • Alanine transaminase (ALT) two times upper limit of normal for age or twofold increase in baseline abnormal ALT
IPSCC = International Pediatric Sepsis Consensus Conference FiO_2: fraction of inspired oxygen; $PaCO_2$: partial pressure of carbon dioxide PaO_2: partial pressure of oxygen.
*International Pediatric Sepsis Consensus Conference definitions Adapted for study by exclusion of criteria of Lactate ≥ 4

SEPTIC SHOCK:
LACTATE AND MORTALITY

In pediatric patients with clinically suspected sepsis in the Emergency Department, is an initial venous lactate of greater than 36 mg/dL (4 mmol/liter) associated with an increased risk of 30-day in-hospital all-cause mortality?

John Park, M.D., Michael Mojica, M.D
November 2017

Scott HF, Brou L, Deakyne SJ, Kempe A, Fairclough DL, Bajaj L.

ASSOCIATION BETWEEN EARLY LACTATE LEVELS AND 30-DAY MORTALITY IN CLINICALLY SUSPECTED SEPSIS IN CHILDREN.

JAMA Pediatr. 2017 Mar 1;171(3):249-255.
PubMed ID: 28068437

STUDY DEFINITIONS	
POPULATION	Inclusion: Colorado Sepsis Treatment and Recognition Registry. Patients identified through the presence of any of the following in the EHR: 1. Use of a sepsis-specific order set in the ED 2. Use of the sepsis activation system in the ED 3. Missed ED cases (see methods for identification process) Exclusion: Age < 60 days or > 18 years Transferred from another medical facility No venous lactate obtained within the first 8 hours of ED arrival Setting: Single, tertiary care free-standing pediatric hospital ED. 4/2012-12/2015 Standardized procedures for sepsis activation, mobilization of personnel and equipment, intravenous access, fluid resuscitation, antibiotics and critical therapeutics. Lactate included in the default order set but could be overridden
TEST	Venous lactate > 36 mg/dL (4 mmol/liter) within 8 hours of arrival (1st specimen) Sub-analysis of lactate > 36 mg/dL (4 mmol/liter) within 2 hours of arrival Sub-analysis of lactate stratified as low (< 18 mg/dl or < 2 mmol/L), intermediate (18-36 mg/dl or 2-4 mmol/L) and high (> 36 mg/dl or > 4 mmol/L)
REFERENCE STANDARD	Primary Outcome: All-cause 30-day mortality after presentation with suspected sepsis Secondary Outcomes: ICU admission, ICU stay > 2 days Intubation, ventilator days Use of vasoactive agents, Days on vasoactive agent Hospital stay > 3 days
OUTCOME	Test characteristics Adjusted odds ratio (Logistic regression) including patient and therapy covariates
DESIGN	Observational: Retrospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. All children with suspicion of sepsis and a lactate within 8 hours were included. However, only 65% of suspected sepsis patients had a venous lactate within 8 hours. Those without a lactate had a 30-day all-cause mortality of 0.6% compared to 1.9% for the included population indicating the possibility of selection bias. It also could be argued that the 19.4% presenting with hypotension did not pose a diagnostic dilemma.
Did investigators compare the test to an appropriate, independent reference standard?	Unclear. The primary outcome was 30-day all-cause mortality. It is unclear how the study verified survival after patients left hospital. This was not discussed in the methods.
Were those interpreting the test and reference standard blind to the other results?	Unknown. Both mortality and lactate are objective and not subject to influence of bias due to lack of blinding. However, an elevated lactate may have been used to guide therapeutic interventions. The authors acknowledge that this could bias the results in the favor of no difference in mortality. Patients with an elevated lactate were significantly more likely to have: sepsis activation, vasoactive infusions and intubation (Table E3 (supplement).
Did all patients regardless patients receive the same reference standard irrespective of the test results?	Yes. An assessment of 30-day all-cause mortality occurred for all patients.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 1,299, male 58%, mean age 7.3 ± 5.3 years
Chronic medical conditions: 69.2%
Central line present: 26%
Acute organ dysfunction: 28.3%
Hypotension: 19.4%
Lactate: Median time survivors (24 min), non-survivors (21 min). All prior to fluids and antibiotics

	30-DAY ALL-CAUSE MORTALITY		
	YES	NO	
Lactate > 36 mg/dl (4 mmol/L)	5	98	103
Lactate ≤ 36mg/dl (4 mmol/L)	20	1,176	1,196
	25	1,274	1,299

TEST CHARACTERISTICS		
CHARACTERISTIC	CALCULATION	% (95% CI)
Prevalence (mortality)	25/1,299	1.9% (1.3, 2.8%)
Sensitivity	5/25	20% (8.9, 39.1%)
Specificity	1,177/1,274	92.3% (90.7, 93.6%)
Predictive Value (+)	5/103	4.9% (2.1, 10.9%)
Predictive Value (-)	1,176/1,196	98.3% (97.4, 98.9%)
Likelihood Ratio (+)	(5/25)/(98/1,274)	2.59 (1.19, 5.83)
Likelihood Ratio (-)	(20/25)/(1,176/1,274)	0.87 (0.71, 1.06)

<u>Association Between Lactate and Mortality</u>
Absolute Odds: All-cause mortality Lactate > 36 mg/dl: 5/98 = 5.1%
Absolute Odds: All-cause mortality Lactate ≤ 36 mg/dl: 20/1,176 = 1.7%
Absolute Odds Difference: 5.1 – 1.7 = 3.4%
Unadjusted Odds Ratio (OR): 5.1/1.7 = 3.0, 95% CI (1.1, 8.2)

Sub-analysis: Lactate < 2 hours: OR: 3.14 (1.15, 8.59)
Sub-analysis: Lactate stratified as Low, Intermediate, High. ↑ Lactate → ↑ Mortality

<u>Regression Analysis (aOR = adjusted Odds Ratio)</u>
Lactate alone: aOR: 3.26, 95% CI (1.2. 9.2)
With the addition of Hypotension: aOR: 2.28, 95% (1.0, 7.8)
With the addition of Chronic complex condition: aOR: 3.69, 95% (1.3, 10.3)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Yes. Lactate an objective lab test and is not subject to interpretation.
Are the study results applicable to the patients in my practice?	Yes. The study included a wide range of patients with suspected sepsis. The high rate of comorbid conditions is similar to our NYU patients.
Will the test results change my management strategy?	No. This study did not aim to change management or posit that lactate should be used to direct care. Lactate should be used as one piece of a very large puzzle.
Will patients be better off as a result of the test?	No. As this will not change management they cannot be better off.

CLINICAL BOTTOM LINE

BACKGROUND: Rapid identification of the patient with sepsis is essential to initiating time sensitive therapeutic interventions. Pediatric systemic inflammatory response vital signs criteria are neither sensitive nor specific. A 2015 analysis revealed a sensitivity of 23%, 95% CI (16, 33%) and specificity of 84.8% (84.5, 85.2%) for requiring a critical care intervention (Scott, Annals EM 2015, PubMed ID: 25778743). The authors concluded that "SIRS vital signs have a low sensitivity for critical illness, making the vital signs poorly suited for use in isolation as a screening test for children requiring resuscitation for sepsis." A lactate level greater than 36 mg/dl (4 mmol/liter) has been proposed as a marker for risk of mortality in adult patients with infection (Shaprio, Annals EM 2005, PubMed ID: 15855951). In a prospective cohort of 239 pediatric patients with sepsis, a serum lactate greater than or equal to 4 mmol/liter was associated with a poor sensitivity of 31%, 95%, CI (13, 58%) for identifying organ dysfunction at 24 hours (Scott, Acad Emerg Med. 2012, PubMed ID: 23167859). The association of lactate with pediatric sepsis mortality has not been firmly established.

CLINICAL QUESTION: In pediatric patients with clinically suspected sepsis in the Emergency Department, is an initial venous lactate of greater than 36 mg/dL (4 mmol/liter) associated with an increased risk of 30-day in-hospital all-cause mortality?

DESIGN/RISK OF BIAS: This was a well-designed observational retrospective cohort of 1,299 pediatric patients with suspected sepsis who had a venous lactate obtained within 8 hours of ED arrival. Only 65% of suspected sepsis patients had a venous lactate within 8 hours. Those without a lactate had a 30 mortality of 0.6% compared to 1.9% for the included population indicating the possibility of selection bias. A lactate level greater than 36 mg/dL (4 mmol/liter) was chose as a cutoff based on adult studies. Lactate level is a continuous variable and it may have been helpful to use receiver operating characteristic curve analysis to identify the accuracy of lactate (area under the ROC curve) and an optimal cutoff for pediatric patients. It could also be argued that the 19.4% of patients presenting with hypotension did not pose a diagnostic dilemma. A sub-analysis of lactate's accuracy in those who were normotensive at presentation may have been helpful. Finally, the method for follow up of patients discharged prior to 30 days was not presented.

PRIMARY RESULTS: The study included 1,299 patients with a 30-day mortality rate of 1.9%, 95% CI (1.3, 2.8%). The majority of patients had a chronic medical condition (69.2%) and 26% had a central line present. 19.4% had hypotension at presentation. Lactate had a poor sensitivity (20%, 95% CI (8.9, 39.1%) for identifying those with 30-day mortality but a reasonable specificity (92.3%, 95% CI (90.7, 93.6%). Essentially, a venous lactate divided a population with a 1.9% risk of 30-day mortality into a high-risk population with 4.9% risk of 30-day mortality if the lactate was greater than 36 mg/dl (4 mmol/L) and a low-risk population with 1.7% risk of 30-day mortality if the lactate was less than or equal to 36 mg/dl (4 mmol/L). The small number of patients who died resulted in wide confidence intervals around the test characteristics.

A venous lactate greater than 36 mg/dl (4 mmol/L) was associated with an increased odds of 30-day all-cause mortality (Unadjusted Odds Ratio 3.0, 95% CI (1.1, 8.2), Adjusted Odds Ratio: 3.26, 95% CI (1.2. 9.2). The addition of hypotension to the regression analysis decreased the adjusted Odds Ratio to 2.28, 95% (1.0, 7.8) and the addition of a chronic complex condition increased the adjusted Odds Ratio to 3.69, 95% (1.3, 10.3). While the odds ratio indicates a statistically significant 3-fold increase in the odds of mortality the absolute difference in odds was small (3.4%). Secondary outcomes were not reported in the manuscript or supplemental materials.

APPLICABILITY: The study's results are based on the experience at single children's hospital. The inclusion of patients with "suspected sepsis" and not only those with "severe sepsis" or "septic shock" likely increased the generalizability of the study's results. However, the population had a high proportion of children with chronic medical conditions (69.2%). While this is likely typical of children's hospital ED patients with suspected sepsis it may not be representative of patients with suspected sepsis in non-children's hospital emergency departments.

AUTHOR'S CONCLUSION: "This study establishes an association between early ED lactate levels and mortality in pediatric sepsis. In addition to prior pediatric work showing that early lactate levels are associated with organ dysfunction and that lactate levels are associated with mortality in the ICU, as well as the demonstrated effectiveness of lactate level measurement in adult sepsis care, this study suggests the possible utility of incorporating lactate level testing in the emergency care of pediatric sepsis. Further studies are needed to examine the effect of the implementation of lactate level testing on patient outcomes in pediatric sepsis."

POTENTIAL IMPACT: Lactate will continue to be useful as a diagnostic tool to gage illness severity and has now been shown as a prognostic indicator for mortality in children. It should be used in conjunction with other diagnostic tests as a part of a large clinical picture to help determine the most appropriate course of treatment.

SEPTIC SHOCK:
NYS SEPSIS BUNDLE COMPLETION

In patients less than 18 years of age in NY state with sepsis or septic shock is the completion of a sepsis bundle consisting of:

1. Broad-spectrum antibiotics initiated within 1 hour of recognition
2. A fluid bolus of 20 ml/kg of crystalloid completed within 1 hour of recognition
3. Blood cultures drawn prior to antibiotic administration

when compared to those with sepsis bundle completion greater than 1 hour and less than 4 hours from sepsis recognition associated with a lower rate of all-cause, in-hospital mortality?

John Park, MD, Dennis Heon, MD
November 2018

Evans IVR, Phillips GS, Alpern ER, Angus DC, Friedrich ME, Kissoon N, Lemeshow S, Levy MM, Parker MM, Terry KM, Watson RS, Weiss SL, Zimmerman J, Seymour CW.

ASSOCIATION BETWEEN THE NEW YORK SEPSIS CARE MANDATE AND IN-HOSPITAL MORTALITY FOR PEDIATRIC SEPSIS

JAMA. 2018 Jul 24;320(4):358-367.
PubMed ID: 30043064

STUDY DEFINITIONS	
POPULATION	Inclusion: < 18 years, sepsis or sepsis shock, only final episode included if > 1 presentation, 1-hour data available from transferring hospital if applicable Exclusion: 1-hour bundle contraindicated, neonates that were never discharged, treatment limited by advanced directives, declined intervention, enrolled in a clinical trial, sepsis bundle completion > 4 hours Setting: 59 acute care hospitals in NY state submitting data, 4/2014-12/2016 ED, inpatient or ICU patients
EXPOSURE	A. Completion of a sepsis bundle within 1 hour of recognition* 1. Administration of broad-spectrum** antibiotics (time administration started) 2. Blood culture obtained prior to antibiotic administration (time obtained) 3. Fluid bolus of 20 ml/kg (time of bolus completion) *Identification criteria varied by institution, **Defined by hospital B. Completion of individual components of the sepsis bundle
NO EXPOSURE	Non-completion of a sepsis bundle between 1 and 4 hours of recognition
OUTCOME	Primary Outcome: All-cause in-hospital mortality Secondary Outcome: Length of stay
DESIGN	Observation: Retrospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	No and Yes. The two patient populations did have some differences as evidenced in Table 1. Notably there were differences in race, co-morbidities, organ dysfunction, site of care (ED, ICU, inpatient) and transfer versus initial presentation for care. Another difference was that facilities with lower pediatric patient volume were less likely to complete the bundle. These differences were accounted for with statistical adjustment in the regression analysis, using matched propensity score analysis and inverse probability weighted regression.
Were the circumstances and methods for detecting the outcome similar?	Yes. All data pertaining to cases of children with sepsis including the outcome of all-cause in-hospital mortality was reported to the NY State Department of Health. There was no other follow up or detection of outcomes.
Was follow-up sufficiently complete?	Yes. No follow up was not needed as the outcome measured was in hospital mortality, not 30 day mortality or similar. This is reasonable as it is to be expected that for those presenting with sepsis, mortality relating to the initial illness should occur during initial hospitalization.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

N = 1,179 (n = 54 hospitals)
Mean Age: 7.2 years
Previously healthy: 44.5%
Crude Mortality:11.8%, Bundle complete: 7.5%, Bundle not complete: 13.2%, Risk difference: 5.7%

BUNDLE COMPLETION	
Blood culture prior to antibiotics	740 (62.8%)
Broad-spectrum antibiotics started within 1 hour	798 (67.7%)
Fluid bolus of 20 ml/kg completed within 1 hour	548 (46.5%)
All 3 bundle components completed with 1 hour	294 (24.9%)
Bundle completion was more common: ED patients, previously healthy patients Bundle completion was less common: Transferred patients	

IN-HOSPITAL MORTALITY: ADJUSTED RISK AND RISK DIFFERENCE (FIGURE 2)			
	Bundle Complete		Adjusted Risk Difference (95%CI)
	YES	NO	
Blood culture prior to antibiotics	10.7%	13.3%	2.6% (-0.5, 5.7%)
Broad-spectrum antibiotics started within 1 hour	11.1%	13.2%	2.1% (-1.1, 5.2%)
Fluid bolus of 20 ml/kg completed within 1 hour	11.2%	12.3%	1.1% (-2.6%, 4.8%)
All 3 bundle components completed within 1 hr*	8.7%	12.7%	4.0% (0.9, 7.0%)
All 3 bundle components completed within 3 hrs			3.6% (0.6, 6.7%)
GREEN = Statistically Significant, RED = Not Statistically Significant			

Covariates in the risk adjustment logistic regression were: Patient age, race, ethnicity, payer, comorbidity burden, location of protocol initiation, site of infection, measures of organ dysfunction including, presence of shock, platelet count, or mechanical ventilation prior to protocol initiation.

IN-HOSPITAL MORTALITY: ADJUSTED ODDS RATIO (FIGURE 2)	
	Odds Ratio (95%CI)
Blood culture prior to antibiotics	0.73 (0.51, 1.06)
Broad-spectrum antibiotics started within 1 hr	0.78 (0.55, 1.22)
Fluid bolus of 20 ml/kg completed within 1 hr	0.88 (0.56, 1.37)
All 3 bundle components completed within 1 hr*	0.59 (0.38, 0.93)
All 3 bundle components completed within 3 hrs	0.64 (0.42, 0.96)
GREEN = Statistically Significant, RED = Not Statistically Significant	

Multiple sensitivity analyses revealed a significant decrease in mortality of the same magnitude as the primary regression analysis.

Figure 3 indicates a “dose-response” effect. In-hospital mortality increased by 2% for each 1-hour delay in bundle completion.

HOW PRECISE IS THE ESTIMATE OF THE RISK?
See confidence intervals for odds ratios and risk differences above The confidence intervals are fairly wide.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Yes. Some of the patients were patients seen at our institution (NYU Medical Center and Bellevue Hospital Center). Data was drawn from 54 hospitals in NY State. This data should be applicable to most of the United States.
Was follow-up sufficiently long?	Yes. The primary outcome was all cause in-hospital mortality. No follow up was needed for this outcome.
Is the exposure similar to what might occur in my patient?	Yes. We follow this bundle as we are located in New York State. We however strive for greater than the 25% of patients with sepsis having completed the bundle that was seen in this study.
What is the magnitude of the risk?	The adjusted risk difference for all cause in-hospital mortality (Bundle not complete – Bundle Complete) was 4.0% (0.9, 7.0%). NNT = 1/ARR = 1/.04 = 25. For every 25 patients with sepsis treated with the 1-hour bundle there will be 1 less in-hospital death.
Are there any benefits that offset the risks associated with exposure?	No. This bundle is becoming the standard of care at most institutions. All of the interventions should be completed in patients presenting with sepsis.

CLINICAL BOTTOM LINE

BACKGROUND: Following the death of a pediatric patient with sepsis in 2013, NY state mandated standards for the treatment of pediatric sepsis. This included blood cultures, broad-spectrum antibiotics, and a 20-mL/kg intravenous fluid bolus completed within one hour of recognition of sepsis. This retrospective cohort study aimed to determine if there was a difference in mortality between those who met the one-hour goal and those who did not.

CLINICAL QUESTION: In patients less than 18 years of age in NY State with sepsis or septic shock is the completion of a sepsis bundle consisting of:
1. Broad-spectrum antibiotics initiated within 1 hour of recognition
2. A fluid bolus of 20 ml/kg of crystalloid completed within 1 hour of recognition
3. Blood cultures drawn prior to antibiotic administration

When compared to those with sepsis bundle completion greater than 1 hour and less than 4 hours from sepsis recognition, associated with a lower rate of all-cause, in-hospital mortality?

DESIGN/RISK OF BIAS: This was a well-designed study retrospective cohort study that included 1,179 pediatric patients with sepsis or septic shock from 54 NY State hospitals. The main risk of bias revolves around how effective the adjustments made for differences between the experimental and control groups were. One concern is that tools to identify sepsis were institution specific and the time from sepsis recognition may not be the best time to start the clock. The primary outcome of all-cause, in-hospital mortality is objective but should be paired with a measure of neurologically intact survival such as the modified Rankin score.

PRIMARY RESULTS: The mean age was 7.2 years and 44.5% of patients were previously healthy. The complete sepsis bundle was completed 24.9% of the time. Individual components of the sepsis bundle were completed 46.5% (fluid bolus), 62.9% (blood culture) and 67.7% (antibiotics) of the time. Bundle completion was more common in ED patients and in previously healthy patients. Bundle completion was less common in transferred patients.

This study demonstrates that the completion of a sepsis bundle including blood culture prior to administration of antibiotics, broad spectrum antibiotic administration and administration of a 20 ml/kg fluid bolus completed within one hour of recognition of sepsis reduced in hospital mortality by 4%. For every 25 patients with sepsis treated with the 1-hour bundle there will be 1 less in-hospital death. The authors did not indicate what they thought was a clinically significant reduction in mortality. The range of bundle completion was 7.3% to 46.1% (median 32.8%, IQR 22.4-37.5%). Hospitals with a higher rate of bundle completion cared for a greater number of pediatric patients and were more likely to have a level 1 pediatric ICU.

Completion of the sepsis bundle also resulted in a decrease in length of stay in in all patients a and survivors (adjusted incidence ratio rate = 0.71, 95% CI (0.60, 0.84) but not in non-survivors.

IN-HOSPITAL MORTALITY: ADJUSTED RISK AND RISK DIFFERENCE (FIGURE 2)			
	Bundle Complete		Adjusted Risk Difference (95%CI)
	YES	NO	
Blood culture prior to antibiotics	10.7%	13.3%	2.6% (-0.5, 5.7%)
Broad-spectrum antibiotics started within 1 hour	11.1%	13.2%	2.1% (-1.1, 5.2%)
Fluid bolus of 20 ml/kg completed within 1 hour	11.2%	12.3%	1.1% (-2.6%, 4.8%)
All 3 bundle components completed within 1 hr*	8.7%	12.7%	4.0% (0.9, 7.0%)
All 3 bundle components completed within 3 hrs			3.6% (0.6, 6.7%)
GREEN = Statistically Significant, RED = Not Statistically Significant			

APPLICABILITY: The inclusion of 54 hospitals in NY State of different types likely makes this study's results generalizable. This study validates that current practice as mandated by New York State has the ability to improve patient outcomes. However, it is unfortunate that the sepsis bundle was completed in only 1 quarter of the patients.

AUTHOR'S CONCLUSION: "In New York State following a mandate for sepsis care, completion of a sepsis bundle within 1 hour compared with not completing the 1-hour sepsis bundle within 1 hour was associated with lower risk-adjusted in-hospital mortality among patients with pediatric sepsis and septic shock."

POTENTIAL IMPACT: While this will not change current practice, it demonstrates the importance of completing this bundle in as many patients with sepsis as possible. Additional efforts should be made to improve the rate of bundle completion.

SEPTIC SHOCK:
PEDIATRICS QSOFA SCORE ACCURACY

In pediatric patients admitted to a non-academic medical center from the Emergency Department and treated with antibiotics for a suspected bacterial infection, does the age-adjusted Quick Sepsis Related Organ Failure Assessment (qSOFA) score, when compared to qSOFA score with Lactate, SIRS criteria and qPELOD-2 score, accurately identify those who require transfer to the PICU or die within 30 days?

Michael Mojica, MD

February 2019

van Nassau SC, van Beek RH, Driessen GJ, Hazelzet JA, van Wering HM, Boeddha NP.

TRANSLATING SEPSIS-3 CRITERIA IN CHILDREN: PROGNOSTIC ACCURACY OF AGE-ADJUSTED QUICK SOFA SCORE IN CHILDREN VISITING THE EMERGENCY DEPARTMENT WITH SUSPECTED BACTERIAL INFECTION.

Front Pediatr. 2018 Oct 1;6:266.
PubMed ID: 30327759

STUDY DEFINITIONS	
POPULATION	Inclusion: < 18, admitted for suspected bacterial infection, treated with antibiotics within 24 hours of ED entry Exclusion: Admitted with a surgical diagnosis Setting: Single, non-academic center (Netherlands), 3/2013-1/2018
TESTS	1. Age adjusted qSOFA score (Quick Sepsis Related Organ Failure Assessment) 2. Age adjusted qSOFA score + Lactate 3. SIRS criteria (Systemic Inflammatory Response Syndrome) 4. qPELOD-2 score (Quick Pediatric Logistic Organ Dysfunction) (See Appendix B for each score's parameters) First measured value within 24 hours of ED arrival Score: ≥ 2 = Positive, < 2 = Negative Missing values: 1 missing value = Assumed normal, > 1 missing value = Missing Lactate (+): > 2 mmol/L
REFERENCE STANDARD	Primary Outcome: Composite of: 1. Transfer to academic center PICU due to cardiorespiratory or neurologic failure 2. Mortality within 30 days Secondary Outcome: Prolonged length of stay (≥ 7 days)
OUTCOME	Test Accuracy: Area under the receiver operating characteristic curve (AUC) Test Characteristics: Sensitivity, specificity, positive and negative predictive values
DESIGN	Observational: Retrospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. Patients were admitted to a non-academic center from the Emergency Department and treated with antibiotics for a suspected bacterial infection. It was not known at that point whether they would require PICU transfer or would die. Data on comorbidities is not presented.
Did investigators compare the test to an appropriate, independent reference standard?	Unclear, the reference standard was a composite of transfer to an academic center PICU or death with 30 days. These are not of equivalent importance. There were only 6 deaths in the study making it difficult to perform a subgroup analysis of each of the variables in the composite outcome.
Were those interpreting the test and reference standard blind to the other results?	Unclear. Clinicians making the decision to transfer a patient to an academic center PICU were likely aware of the clinical parameters used to calculate the score. Timing is provided for when each of the parameters was initially evaluated but the timing of the PICU transfer decision or time of death in relation to when the parameters were measured is not provided.
Did all patients receive the same reference standard irrespective of the test results?	Yes. The study assessed the accuracy of each of the scores to predict transfer to PICU or death.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 864, Age: Median 2.5 years, IQR (9 month, 6 years)

Primary Outcome
PICU Transfer OR Death within 30 days: 23/864 (2.7%)
Death within 30 days: 6/864 (0.7%)
PICU Transfer: 18/864 (2.1%)

PRIMARY OUTCOME: PICU TRANSFER AND/OR DEATH

SCORE	AUC (95%CI)	SN	SP	NPV	PPV
qSOFA	0.72 (0.57, 0.86)*	50.0%	93.3%	98.0%	22.5%
qSOFA + Lactate	0.67 (0.50, 0.84)	58.3%	76.3%	95.5%	17.5%
SIRS	0.64 (0.53, 0.74)	81.8%	45.8%	98.8%	4.3%
qPELOD-2	0.60 (0.45, 0.76)	22.2%	98.7%	97.4%	36.4%

*qSOFA had a significantly higher AUC than qSOFA + Lactate and qPELOD-2 but not SIRS
95% confidence intervals for test characteristics were not provided

qSOFA SCORE COMPONENT PERFORMANCE (AUC (95%CI))

Total Score (Positive ≥ 2)	0.72 (0.57, 0.86)
Systolic Blood Pressure	0.56 (0.39, 0.74)
Level of Consciousness	0.74 (0.58, 0.90)
Respiratory Rate	0.54 (0.43, 0.66)

SECONDARY OUTCOME: LENGTH OF STAY > 7 DAYS (22%)

SCORE	AUC (95%CI)	SN	SP	NPV	PPV
qSOFA	0.53 (0.46, 0.59)	5.8%	89.0%	21.6%	64.5%
qSOFA + Lactate	0.56 (0.46, 0.67)	21.2%	65.9%	30.2%	54.5%
SIRS	0.49 (0.44, 0.54)	55.0%	47.7%	22.2%	79.6%
qPELOD-2	0.51 (0.45, 0.57)	1.0%	97.3%	22.3%	57.1%

No statistically significant difference for qSOFA AUC compared to any of the other scores
95% confidence intervals for test characteristics were not provided

See Appendix A for missing data for each score parameter and total score

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Unclear. qSOFA includes an assessment of blood pressure, respiratory rate and mental status. Blood pressure and respiratory rate of relatively objective. Assessment of mental status by AVPU is also fairly objective but the pediatric GCS may be more subjective. As a retrospective cohort study, inter-rater reliability on these parameters could not be assessed.
Are the study results applicable to the patients in my practice?	Unclear. This was a very narrow subset of patients admitted from the ED to a non-academic medical center in the Netherlands. Co-morbid conditions were not presented. Unclear if a non-academic hospital population in the Netherlands is generalizable to an equivalent setting in the US.
Will the test results change my management strategy?	No. There are a number of design, results and applicability issues that make it difficult to interpret and apply the study's results. If the results can be trusted, qSOFA did not perform better than SIRS criteria but has the advantage that all parameters can be obtained at the bedside and does not include a laboratory result.
Will patients be better off as a result of the test?	Early identification of sepsis and initiation of goal directed therapy is associated with improved outcomes. In addition, identification of those at low risk would precluded the use of goal directed therapy unnecessarily.

CLINICAL BOTTOM LINE

BACKGROUND: Early identification of sepsis and initiation of goal directed therapy is associated with improved outcomes. A combination of abnormal vital signs, physical exam findings, patient characteristics and laboratory parameters were previously recommended by the surviving sepsis guidelines to identify those with sepsis. However, systemic inflammatory response system (SIRS) vital signs were found to be neither sensitive nor specific in the pediatric population (Scott, Academic EM 2015, PubMed ID: 25778743). 15% of pediatric non-trauma patients met SIRS vital signs criteria while only 0.25% required a critical care intervention. SIRS vital signs identified only 23%, 95% CI (16, 33%) of those requiring a critical care intervention. As a result, The 2017 pediatric surviving sepsis guidelines acknowledge that there is insufficient evidence to endorse a specific sepsis trigger tool and recommend that each institution develop their own recognition bundle (Amer College Critical Care, Critical Care Medicine 2017, PubMed ID: 28509730).

The sepsis 3 guidelines recommended the use the Sepsis Related Organ Failure Assessment (SOFA) score for early identification of sepsis in adults (Singer, JAMA 2016, PubMed ID: 26903338). An abbreviated version of SOFA (Quick SOFA or qSOFA) which includes variables available at the bedside in the ED (systolic BP, respiratory rate and mental status) was also recommended. SOFA and qSOFA has been found to have greater diagnostic accuracy than SIRS in adults. An age adjusted qSOFA has been studied in the pediatric ICU but not in the ED setting.

CLINICAL QUESTION: In pediatric patients admitted to a non-academic medical center from the Emergency Department and treated with antibiotics for a suspected bacterial infection, does the age-adjusted Quick Sepsis Related Organ Failure Assessment (qSOFA) score, when compared to qSOFA score with Lactate, SIRS criteria and qPELOD-2 score, accurately identify those who require transfer to the PICU or die within 30 days?

DESIGN/RISK OF BIAS: This was a retrospective cohort study conducted at a single non-academic center in the Netherlands. Patients under 18 were included is they were admitted from the ED with a suspected bacterial infection which was defined as receiving antibiotics within 24 hours of ED arrival. The proportion of patients receiving antibiotics in the ED was not presented. Surgical patients were excluded. There was no confirmation of bacterial infection. The study assessed the accuracy of 4 scores (qSOFA, qSOFA + Lactate, SIRS and qPELOD-2) in identifying the composite outcome of transfer to an academic center PICU or death within 30 days. These 2 reference standards are not of equal importance.

Clinicians making the decision to transfer a patient to an academic center PICU were likely aware of the clinical parameters used to calculate the score. Timing is provided for when each of the parameters was initially evaluated but the timing of the PICU transfer decision or time of death in relation to when the parameters were measured is not provided.

PRIMARY RESULTS: The study included 864 patients with a median age of 2.5 years, IQR (9 month, 6 years). There were few patients with the primary outcomes of PICU transfer OR death within 30 days: 23/864 (2.7%). There was a significant proportion of patient with missing data (See Appendix A). The qSOFA score had moderate predictive ability with an area under the receiver operating characteristic curve (AUC) of 0.72, 95% CI (0.57, 0.86). qSOFA had a significantly higher AUC than qSOFA + Lactate (0.67, 95% CI (0.50, 0.84)) and qPELOD-2 (0.60, 95% CI (0.45, 0.76) but not significantly higher than

SIRS (0.64, 95% CI (0.53, 0.74). AUC curves cross for qSOFA and SIRS making any interpretation of differences in AUC difficult (Figure 2). Of the qSOFA parameters, level of consciousness had the highest AUC (0.74, 95% CI (0.58, 0.90)) compared to systolic blood pressure (0.56, 95% CI (0.39, 0.74)) and respiratory rate (0.54, 95% CI (0.43, 0.66)).

qSOFA stratified a group of patients with a with a 2.7% risk of ICU Transfer or Death within 30 days into a high risk group (22.5%) if qSOFA was positive (≥ 2 parameters)and a low risk group (2%) if qSOFA was negative (< 2 parameters). qSOFA would not identify half of the patients with the outcome (Sensitivity 50%) and would misidentify 6.3% of the patients without the outcome (1-Specificity). 95% confidence intervals for test characteristics were not provided.

PRIMARY OUTCOME: DEATH OR PICU TRANSFER					
SCORE	AUC (95%CI)	SN	SP	NPV	PPV
qSOFA	0.72 (0.57, 0.86)*	50%	93.3%	98.0%	22.5%
qSOFA + Lactate	0.67 (0.50, 0.84)	58.3%	76.3%	95.5%	17.5%
SIRS	0.64 (0.53, 0.74)	81.8%	45.8%	98.8%	4.3%
qPELOD-2	0.60 (0.45, 0.76)	22.2%	98.7%	97.4%	36.4%
qSOFA had a significantly higher AUC than qSOFA + Lactate and qPELOD-2 but not SIRS 95% confidence intervals for test characteristics were not provided					

APPLICABILITY: This was a very narrow subset of patients admitted from the ED to a non-academic medical center in the Netherlands. Co-morbid conditions were not presented. It is unclear if a non-academic hospital population in the Netherlands is generalizable to an equivalent setting in the US.

Blood pressure and respiratory rate of relatively objective. Assessment of mental status by AVPU is also fairly objective but the pediatric GCS may be more subjective. As a retrospective cohort study, inter-rater reliability on these parameters could not be assessed.

AUTHOR'S CONCLUSION: "In conclusion, this is the first study to assess qSOFA criteria in a pediatric ED population. Since we compared qSOFA with other prognostic scores, our study contributes to current attempts to translate sepsis-3 criteria to children. qSOFA shows moderate prognostic accuracy for PICU transfer and/or mortality. The prognostic accuracy of qSOFA tends to be higher than SIRS and is significantly higher than qPELOD-2. Prognostic accuracy of qSOFA did not improve after inclusion of lactate. Prospective multicenter studies in larger ED populations of febrile children should be performed to further determine the utility of the qSOFA score in the pediatric ED. Pediatric sepsis researchers should assure that pediatric Sepsis-3 criteria are applicable to ED patients as well."

POTENTIAL IMPACT: There are a number of design, results and applicability issues with this study ultimately making it difficult to interpret and apply its results. If the results can be trusted, qSOFA did not perform better than SIRS criteria but has the advantage of not including a laboratory result. It would be essential to validate qSOFA in a prospective, multicenter cohort including all febrile ED patients.

The 2017 pediatric surviving sepsis guidelines acknowledge that there is insufficient evidence to endorse a specific sepsis trigger tool and recommend that each institution develop their own recognition bundle (Amer College Critical Care, Critical Care Medicine 2017, PubMed ID: 28509730).

APPENDIX A: MISSING DATA

MISSING DATA: PARAMETERS (TEXT), SCORES AND FIGURE 1)				
Parameter	Missing Data	Time from ED Arrival	Score	Missing (%)
Respiratory Rate	22%	29 min	qSOFA	> 40%
Heart Rate	9%	24 min	qSOFA + Lactate	> 80%
Blood Pressure	69%	86 min	SIRS	> 10%
Temperature	1%	24 min	qPELOD-2	> 30%
Mental Status	51%	34 min		
WBC	23%	65 min		
Lactate	96%	71 min		

APPENDIX B: SCORE PARAMETERS

COMPARISON: SCORE PARAMETERS				
	qSOFA	qSOFA + Lactate	SIRS	qPELOD-2
Respiratory Rate	X	X	X	
Heart Rate			X	X
Blood Pressure	X	X		X
Temperature			X	
Mental Status	X	X		X
WBC			X	
Lactate		X		

qSOFA: QUICK SEPSIS RELATED ORGAN FAILURE ASSESSMENT			
	AGE	SCORE 0	SCORE 1
Respiratory Rate	0 days – 1 week	50	> 50
	1 week – 1 month	40	> 40
	1 month – 1 year	34	> 34
	2-5 years	22	> 22
	6-12 years	18	> 18
	13-7 years	14	> 14
Altered Mental Status (AVPU or Pediatric GCS)	0 days – 18 years	A	V, P, U
	0 days – 18 years	15	< 15
Systolic Blood Pressure	0 days – 1 week	≥ 59	< 59
	1 week – 1 month	≥ 79	< 79
	1 month – 1 year	≥ 75	< 75
	2-5 years	≥ 74	< 74
	6-12 years	≥ 83	< 83
	13-17 years	≥ 90	< 90
qSOFA + Lactate	0 days – 18 years	< 2 mmol/L	≥ 2 mmol/L

SIRS: SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			
	AGE	SCORE 0	SCORE 1
Heart Rate	0 days – 1 week	100-180	> 180 or < 100
	1 week – 1 month	100-180	> 180 or < 100
	1 month – 1 year	90-180	> 180 or < 90
	2-5 years	< 140	> 140
	6-12 years	< 130	> 130
	13-7 years	< 110	> 110
Respiratory Rate	0 days – 1 week	< 50	> 50
	1 week – 1 month	< 40	> 40
	1 month – 1 year	< 34	> 34
	2-5 years	< 22	> 22
	6-12 years	< 18	> 18
	13-7 years	< 14	> 14
Leukocyte Count	0 days – 1 week	< 34	> 34
	1 week – 1 month	5-19.5	> 19.5 or < 5
	1 month – 1 year	5-17.5	> 17.5 or < 5
	2-5 years	6-15.5	> 15.5 or < 6
	6-12 years	4.5-13.5	> 13.5 or < 4.5
	13-7 years	4.5-11	> 11 or < 4.5
Temperature	0 days – 18 years	36-38.5	> 38.5 or < 36

qPELOD-2: QUICK PEDIATRIC LOGISTIC DYSFUCTION-2					
		SCORE 0		SCORE 1	
	AGE	SBP	MAP	SBP	MAP
Hypotension	0 days – 1month	> 65	> 46	< 65	< 46
	1-11 months	> 75	> 55	< 75	> 55
	12-23 months	> 85	> 60	< 85	< 60
	24-59 months	> 85	> 62	< 85	< 62
	60-143 months	> 85	> 65	< 85	< 65
	≥ 144 months	> 95	> 67	< 95	< 67
Heart Rates	< 12 years	< 195		> 195	
	≥ 12 years	< 150		> 150	
Mental Status (Ped GCS)	0 days – 18 years	> 11		< 11	

SEPTIC SHOCK:
PEDIATRICS SIRS CRITERIA

In consecutive non-trauma patients < 18 years of age presenting to the emergency department, is the presence of Systemic Inflammatory Response (SIRS) vital signs when compared to those without SIRS vital signs accurate in identifying those both with and without critical illness within 24 hours?

Joshua Beiner, M.D., Adriana Manikian, M.D.
July 7, 2015

Scott HF, Deakyne SJ, Woods JM, Bajaj L.

THE PREVALENCE AND DIAGNOSTIC UTILITY OF SYSTEMIC INFLAMMATORY RESPONSE SYNDROME VITAL SIGNS IN A PEDIATRIC EMERGENCY DEPARTMENT.

Acad Emerg Med. 2015 Apr;22(4):381-9.
PubMed ID: 25778743

STUDY DEFINITIONS	
POPULATION	Inclusion: Patients <18 years of age who stayed through completion of evaluation Exclusion: Isolated trauma diagnosis or missing SIRS vital signs documentation Setting: Single tertiary care Pediatric ED. 4/2011-3/2012
TEST	SIRS VS as a predictor for Critical Care SIRS VS defined as fever with an abnormal BP, corrected HR or RR (Did not include WBC or CRP which are included in Adult SIRS criteria because they are not available at the time of triage)
REFERENCE STANDARD	Patients meeting critical care primary outcome defined as receipt of vasoactive agent or intubation within 24 hours of ED arrival
OUTCOME	Primary Outcome: Test Characteristics of SIRS vital for detecting Critical Care Secondary Outcomes: Prevalence of SIRS vital signs Severity of illness in patients with SIRS vital signs ICU Admission 30-day in-hospital mortality 72-hour readmission to inpatient service ED lab evaluation ED intravenous therapy Predictive value of various SIRS VS combinations for critical care.
DESIGN	Observational: Retrospective Cohort study

ARE THE RESULTS VALID?	
Did participating patients present a diagnostic dilemma?	Yes. Sepsis is a leading cause of pediatric mortality, with reported rates reaching 10%. While international consensus guidelines exist for management of pediatric septic shock, there are no standardized triage and work-up protocols for early detection of severe sepsis and septic shock in children. Adult and pediatric guidelines both emphasize early detection of severe sepsis and septic shock and rapid implementation of treatment practices. As SIRS is part of the adult definition of sepsis and has been used in many of the landmark studies and Surviving Sepsis campaign, it has similarly been recommended as a tactic for detection of pediatric sepsis.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The authors compared SIRS vital signs to an outcome of Critical Care defined as receipt of vasoactive agents and/or intubation. Cardiovascular dysfunction or ARDS independently or in combination sufficiently meet criteria for septic shock. Respiratory system abnormalities not meeting full ARDS definitions may help contribute to a diagnosis of severe sepsis, which also requires PALS or American College of Critical Care Medicine (ACCM) Septic Shock protocoled management. These are the patients, rather than those that just meet 'sepsis' criteria that we want to identify early, and provide early therapy.
Were those interpreting the test and reference standard blind to the other results?	No. However blinding for this study would not be expected to significantly bias outcomes as long as providers administered vasoactive medications and intubated patients according to standard indications. Vital signs were taken retrospectively from the electronic medical record and it can be assumed that regardless of whether the Critical Care outcome occurred in the ED or PICU, the participating providers were aware of the vital signs.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	Yes and No. All patients were eligible for the reference standard of Critical Care outcome. However, the vast majority of patients did not receive vasoactive medications or intubation. 90% of children were discharged home, including 83% of those with (+) SIRS vital signs, so it is possible that Critical Care outcome was missed if the child represented to another hospital. The 72-hour Inpatient Readmission rate of 0.93% suggests that this was not a common occurrence.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

		REQUIRED CRITICAL CARE		
		YES	NO	
ANY SIRS VITAL SIGNS	YES	23	6,099	6,122
	NO	76	34,158	34,234
		99	40,257	40,356

Prevalence (Any SIRS VS) = 6,122/40,356 = 15.2% (93% of those with fever met SIRS VS)
Prevalence (Critical care) = 99/40,356 = 0.25% (1 in 400)

Sensitivity: 23/99 = 23%, 95% CI (16, 33%)
Specificity: 34,158/40,257 = 84.8%, 95% CI (84.5, 85.2%)
Predictive Value (+) Test: 23/6,122 = 0.004%, 95% CI (0.003, 0.006%)
Predictive Value (-) Test: 34,158/34,234 = 99.8%, 95% CI (99.7, 99.8%)
Likelihood Ratio (+) Test: ((23/99)/(6,099/40,257) = 1.53, 95% CI (1.07, 2.19)
Likelihood Ratio (-) Test:(76/99)/(34,158/40,257) = 0.91, 95% CI (0.812, 1.01)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	Yes. NY has recently mandated pediatric sepsis screening, but the method for doing so is not yet standardized. Since consensus definitions of pediatric SIRS, sepsis, severe sepsis, and septic shock are relatively new, the rates of each are not yet known with confidence. Over 15% of the eligible population met SIRS criteria, which is close to the range previously reported of 20%.
Are the study results applicable to the patient in my practice?	A significant proportion of pediatric ED visits are those for febrile illnesses, and 93% of febrile children in this study also met SIRS criteria. Between our two hospital sites we care for thousands of patients annually with febrile illnesses including those with complex medical conditions often followed in tertiary care centers.
Will the results change my management strategy?	This study, especially if replicated, is further evidence that SIRS vital signs when taken in isolation should be considered insufficient information for mandating further testing or resuscitative interventions. The test did little to significantly risk-stratify patients by altering post-test probability. In this study, patients entered with a 0.25% (1 in 400) pre-test probability for the critical care outcome. The presence of SIRS vital signs results in a post-test probability of 0.38% (1 in 263) and the absence of SIRS vital signs results in a posttest probability 0.22% (1 in 455). Neither of these values appears to be sufficiently different from the pre-test probability to alter management in any meaningful way. SIRS vital signs are their own are insufficient to either rule in or rule out sepsis and should be interpreted in the context of other factors such as the patients risk of infection, readily available laboratory tests (e.g. WBC and Lactate) and clinical finding of hypoperfusion.
Will patients be better off as a result of the test?	Sepsis alerts may be beneficial in that highlighted vital sign abnormalities call a provider's attention to those who could be significantly ill. This might be especially useful to inexperienced providers, those providers uncertain of age-specific normal ranges, and busy attendings/nurses who can then direct more attention to particular patients. However, lack of SIRS vital signs does not ensure health, as evidenced by the fact that >75% of patients with Critical Care outcome were negative for any SIRS vital signs. Ill or toxic-appearing patients on exam with suspected infection should enter the Septic Shock algorithm regardless of vital signs, and those initially considered to have mild infections should be reassessed during management.

CLINICAL BOTTOM LINE

BACKGROUND: Severe sepsis and septic shock is a major cause of pediatric morbidity and mortality, and the pediatric section in Surviving Sepsis clinical guidelines reiterate previous studies suggesting that early recognition, fluid resuscitation, and antibiotics are mortality-reducing measures. SIRS criteria and the relation to severe sepsis and septic shock is more established in the adult literature, however, the pediatric recommendations are not as clear. In children, definitions of SIRS, sepsis, severe sepsis, and septic shock are newer, the rate of SIRS vital signs in all-comers to the ED appears higher in children, and the strength of the relation between those with SIRS criteria and those who will develop severe sepsis or septic shock is not as apparent.

CLINICAL QUESTION: In consecutive non-trauma patients <18 years of age presenting to the emergency department, is the presence of Systemic Inflammatory Response (SIRS) vital signs when compared to those without SIRS vital signs accurate in identifying those both with and without critical illness within 24 hours?

DESIGN/VALIDITY: This was a retrospective cohort study including over 40,000 patients with over 6,000 meeting SIRS criteria of any vital sign but less then 100 requiring critical care. The primary outcome was the detection of a critical rare outcome defined as receipt of a vasoactive infusion or intubation within 24 hours of ED arrival. While this might not be the traditional reference standard for sepsis, which often focuses on ICD-9 codes, billing codes, or (+) blood cultures, this definition is relevant because intubation and receipt of vasoactive agents are surrogates for cardiovascular and respiratory organ system dysfunction, respectively. Cardiovascular dysfunction or acute respiratory distress syndrome independently meets criteria for septic shock, It is these patients who would benefit from early detection, resuscitation, and treatment. Most febrile patients with SIRS criteria will meet the definition of Sepsis unless the fever is of suspected to be of a non-infectious etiology.

There are standardized indications for use of vasoactive agents like mean arterial blood pressure, minimum systolic blood pressure and persistent signs of poor perfusion after appropriate fluid resuscitation. The initiation of intubation or vasoactive infusions is likely based on relatively objective criteria. Admission to ICU or ICU length of stay (LOS) is more likely to be provider-dependent or hospital-resource dependent, or bed-availability-dependent.

The downside of this definition is that while SIRS is generally used to detect patients who might have severe sepsis or septic shock, vasoactive medications and intubation are not entirely specific for these outcomes. The critical care outcome in this study may overestimate the prevalence of critical illness.

PRIMARY RESULTS: Approximately 16.3% (n=6,596) of the sample had fever > 38.5C, and 92.8% (n=6,122) of these febrile patients met SIRS vital sign criteria. Despite the high rate of SIRS vital signs, a critical care" outcome was extremely rare (0.25%) overall, but statistically significantly higher in those meeting SIRS vital signs criteria (0.38%) than those not meeting SIRS vital signs criteria (0.22%) (RR 1.69, 95% CI, (1.06, 2.70). With the exception of 30-day mortality, rates of all secondary outcomes were significantly higher in the group meeting SIRS vital signs criteria. Absolute rate differences were small and likely not clinically significant. Of those with a critical care outcome, significantly more patients meeting SIRS vital signs criteria received vasoactive agents. Those not meeting SIRS vital signs criteria were more often due to intubation.

While ‘Temperate + Corrected HR” were the most predictive combination of SIRS vital signs for critical care outcome, test characteristics were almost identical with any pair of vital signs abnormalities. Sepsis alerts are generally thought of as sensitive screening tools to cast a broad net in order to detect early on those patients who might have more serious infections. This study shows that no combination of SIRS criteria was adequately sensitive for the outcome, and that SIRS vital signs missed more than 75% of those with Critical Care outcome. Despite the high specificity to “Rule-In” disease, only 0.37% of those (+) for SIRS will be expected to have the outcome.

APPLICABILITY: The biggest potential limitation is that not every patient had admission, monitoring, or follow-up to the 24-hour mark that defined the primary critical care outcome. The overall low prevalence of the primary outcome and low 72-hour readmission rate suggests that few, if any, patients with critical care outcome were missed. However, it is feasible that discharged patients subsequently sought care in outside hospitals. It is unlikely that early treatment with intravenous or antibiotics prevented a significantly higher rate of critical care as only 8% of those with SIRS vital signs received intravenous medications or fluids in the ED.

AUTHOR’S CONCLUSIONS: “Patients with SIRS vital signs represented 15.2% of complete medical ED visits with vital signs recorded at a tertiary pediatric hospital, and the majority of patients with these vital signs were discharged without intravenous therapy and without readmission. Patients with systemic inflammatory response syndrome vital signs had statistically significant and clinically modest increased risks of critical care, admission, and ED intervention. However, SIRS vital signs have a low sensitivity for critical illness, making the vital signs poorly suited for use in isolation as a screening test for children requiring resuscitation for sepsis.”

POTENTIAL IMPACT: Overall, this study lends support to the idea that SIRS vital signs alone are insufficiently predictive of severe infection in children. As a result, it would be imprudent to mandate further laboratory management, treatment, and admission of every patient meeting SIRS vital signs criteria. If similar screening protocols continue, then well-appearing patients without exam signs of severe sepsis or septic shock and those who improve with supportive measures should not proceed to PALS/ACCM Shock protocols. The SIRS vital signs may be beneficial by alerting providers unaware of age-specific vital signs of a potentially ill patient, prompting a quick assessment of such patients, and directing resources to those patients determined to be at risk of significant infection.

RHEUMATOLOGY

1. Kawasaki Disease: Corticosteroids: JAMA Pediatr. 2016

KAWASAKI DISEASE: CORTICOSTEROIDS

In pediatric patients with Kawasaki disease, does the addition of Corticosteroids as initial or rescue therapy to intravenous immune globulin (IVIG) and Aspirin, reduce the incidence of coronary artery complications?

Michael Mojica, M.D.
May 2017

Chen S, Dong Y, Kiuchi MG, Wang J, Li R, Ling Z, Zhou T, Wang Z, Martinek M, Pürerfellner H, Liu S, Krucoff MW.

CORONARY ARTERY COMPLICATION IN KAWASAKI DISEASE AND THE IMPORTANCE OF EARLY INTERVENTION.

JAMA Pediatr. 2016 Dec 1;170(12):1156-1163.
PubMed ID: 27749951

STUDY DEFINITIONS	
POPULATION	Inclusion: Studies of children with Kawasaki disease. Exclusion: None presented Setting: Studies published 1999-2013, most conducted in Japan
INTERVENTION CONTROL 1	Initial Therapy Intervention: Corticosteroids and Intravenous Immune Globulin (IVIG) Control: Intravenous Immune Globulin
INTERVENTION CONTROL 2	Rescue Therapy Intervention: Corticosteroids after IVIG resistance (Persistent or recurrent fever or relapse within 24-48 hours) Control: Intravenous immune globulin after IVIG resistance
CO-INTERVENTIONS	Oral Salicylates
OUTCOME	Primary Outcome: Incidence of coronary artery aneurysm by echocardiogram 1. Japanese Ministry of Health Criteria: Coronary artery internal lumen diameter > 3 mm if < 5 years or > 4 mm if ≥ 5 years 2. Z score System: Z-score > 2.5 or 3 standard deviations for age Secondary Outcomes: Time to defervescence Adverse events as defined by individual studies
DESIGN	Meta-analysis of comparative trials

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review include explicitly and appropriate eligibility criteria?	Yes. Criteria for study inclusion were clearly defined.
Was biased selection and reporting of studies unlikely?	Yes. Medline, the Cochrane Library, and the Clinicaltrials.gov were searched until 7/2015. The search terms were provided. English and non-English articles were included. There was a low risk of publication bias (statistical index of fail-safe N = 74 (*P* = .56) and Begg regression test with an intercept of −0.85 (*P* = .25).
Were the primary studies of high methodologic quality?	Study characteristics (study purpose, study design, inclusion, and exclusion criteria); participant characteristics (age, sex, race/ethnicity, and severity of illness); information of the intervention (treatment preparation, dose, and duration); and assessment of outcome (method, criteria, incidence, and adverse events) were extracted by 2 investigators. 8 studies were randomized clinical trials. The other 8 studies were non-randomized comparative studies. Methodological quality of the 16 studies was good. The authors used a 7-point scale. The mean score was 5.7 out of 7 with a lowest score of 5 out of 7. The most common potential biases were lack of randomization and blinding.
Were assessment of studies reproducible?	Titles and abstracts were reviewed by 2 authors (S.C. and Y.D.) to determine suitability for inclusion. Discrepancies were resolved by consensus. Inter-rater reliability for study inclusion and study quality were not provided.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

Heterogeneity was assessed qualitatively by the *Q* test and quantitatively by the value I^2 statistic. A random-effects regression model was used to combine study data. All study comparison demonstrated modest heterogeneity across included studies (*P* = .10; I^2 = 32.9%).

WHAT ARE THE OVERALL RESULTS OF THE REVIEW? DID THE REVIEW ADDRESS CONFIDENCE IN EFFECT ESTIMATES?

N = 16 studies, Initial (10), Rescue (6)
(4 of Initial studies with high risk of resistance patients)
2,746 patients (Corticosteroids: 861, IVIG: 1,885)

PRIMARY OUTCOME:

RISK OF ARTERY ANOMALIES CORONARY	
	Odds Ratio* (95% CI)
All studies	0.42 (0.27, 0.67)
Initial (All patients)	0.32 (0.18, 0.56)
Initial (High risk patient)	0.24 (0.12, 0.47)
Rescue	0.85 (0.47, 1.56)
*Odds ratio (corticosteroids/no corticosteroids)	

Secondary Outcome: Time to Defervescence
Corticosteroids: 0.66 ± 1.08 days
IVIG: 2.81 ± 2.55 days
Risk Difference: 1.80 days, 95% CI (0.09, 1.80 days)

Secondary Outcome: Adverse Events
Corticosteroids: 8%
IVIG: 7.7%
Odds Ratio: 1.31, 95% CI (0.49, 3,49)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were all patient-important outcomes considered?	The outcome of primary concern in Kawasaki disease is the development of coronary aneurysms as this is associated with a high risk of later coronary syndromes. The rate of adverse events was reported but the type of adverse events was not reported. The long-term consequence of coronary anomalies was not assessed in any of the included studies.
Are any postulated subgroup effects credible?	Yes. It makes sense that those at highest risk for defervescence demonstrated a greater benefit of corticosteroids. It also makes sense the early treatment intervening in the acute inflammatory phase would be beneficial. It would have been helpful to provide the analysis for those patients not at high risk for resistance, a sensitivity analysis comparing randomized to non-randomized clinical trials and an analysis comparing the Prednisone/Prednisone to Methylprednisolone
Are the benefits worth the costs and potential risks?	It appears that corticosteroids decrease the development of coronary aneurysms in all patients and high-risk patients treated with corticosteroids initially. There was no difference in adverse events though this was not reported separately for the studies of initial versus rescue therapy.

CLINICAL BOTTOM LINE

BACKGROUND: Kawasaki disease is a systemic vasculitis occurring primarily in infants and children and is the most common cause of acquired heart disease in children. Many children develop coronary artery dilation in the acute phase. In untreated patients, coronary artery aneurysms and ectasia can develop and result in an increased risk of coronary complications such as myocardial infarction. The primary treatment of Kawasaki disease is a combination of intravenous immune globulin (IVIG) and Aspirin. However, many patients are resistant to this therapy resulting in an increased risk of coronary artery malformations. The anti-inflammatory effects of corticosteroids have been demonstrated to be beneficial on other types of vasculitis. Non-randomized trials have demonstrated conflicting evidence of the benefit of corticosteroids in Kawasaki disease. The role of corticosteroids as initial or rescue therapy has not been conclusively established.

CLINICAL QUESTION: In pediatric patients with Kawasaki disease does the addition of corticosteroids as initial or rescue therapy to intravenous immune globulin and Aspirin reduce the incidence of coronary artery complications?

DESIGN/RISK OF BIAS: This was a meta-analysis of both randomized and non-randomized clinical trials. It included 16 comparative studies (17 study arms) with 2,746 patients. The search was extensive and there was no evidence of publication bias. However, assessment of inter-rater reliability for study inclusion and quality was not presented. Included studies were of high quality with a mean score of 5.7 out of 7.

There are several validity concerns. 3 different corticosteroids were utilized in the studies: Prednisone/ Prednisolone, Dexamethasone and Methylprednisolone. A 2 mg/kg/day dose of Prednisone/ Prednisolone dose is not equivalent to 30 mg/kg/day of Methylprednisolone (Glucocorticoid equivalency Prednisone:Methylprednisolone = 4:5). The studies also utilized 2 different criteria for coronary dilatation. It is unclear if they are equivalent. The secondary outcomes appear to be provided for both studies of initial and rescue corticosteroids therapy and not separately for each group. In addition, 3 different scoring systems are used to identify those at high risk of IVIG resistance. These were developed with Japanese children possible limiting their generalizability to other populations.

PRIMARY RESULTS: There was a significant reduction in the development of coronary artery anomalies in those treated with Corticosteroids and IVIG as initial therapy when compared to those treated with IVIG alone (Odds Ratio: 0.32, 95% C((0.18, 0.56)). This effect was most pronounced in patients assessed as high risk of resistance (Odds Ratio: 0.24, 95% CI (0.12, 0.47)). It is unclear if a benefit remained when analyzing the subgroup of patients that was not at high risk of resistance. There was also an inverse relationship between the efficacy of corticosteroids and time to initiation. It is unclear if studies on the use of rescue corticosteroids were included in this analysis. There was no benefit of corticosteroids when utilized as rescue therapy

CORTICOSTEROID EFFECT ON CORONARY ANEURYSMS	
Study Groups	Odds Ratio* (95% CI)
All studies	0.42 (0.27, 0.67)
Initial Therapy (All patients)	0.32 (0.18, 0.56)
Initial Therapy (High risk patients)	0.24 (0.12, 0.47)
Rescue Therapy	0.85 (0.47, 1.56)
*Odds Ratio = Corticosteroids/No Corticosteroids	

It appears as if the analysis of secondary outcomes was presented for corticosteroids used as initial and rescue therapy combined. There was a statistically significant decrease in the time defervescence in the Corticosteroid group (Risk Difference: 1.80 days, 95% CI (0.09, 1.80 days)). There was no difference in the rate of adverse events when comparing Corticosteroids (8.0%) and No Corticosteroids (7.7%). Odds Ratio: 1.31, 95% CI (0.49, 3,49). However, the actual adverse events were not reported.

APPLICABILITY: Most studies were conducted in Japan where the higher prevalence of KD may result in earlier diagnosis and treatment. It is unclear if study results can be generalized to patients who are not at high risk of IVIG resistance. It would have been helpful to conduct subgroup analyses comparing randomized to non-randomized clinical trials and studies using Prednisolone/Prednisolone to those using Methylprednisolone.

AUTHOR'S CONCLUSION: "This systematic review and meta-analysis collected data from a large sample of 16 clinical studies involving 2,746 cases to give an updated evaluation of 2 different strategies in treating Kawasaki disease and preventing coronary abnormalities. Corticosteroids combined with Intravenous immune globulin as an initial therapy showed a more protective effect compared with conventional Intravenous immune globulin therapy, and the efficacy was more pronounced in high-risk patients at the initiation of intervention, indicating that an early and aggressive initial anti-inflammation therapy for high-risk patients may be beneficial to improve coronary outcomes. Corticosteroid therapy strategy was also correlated with a more rapid resolution of fever, and the merit of corticosteroids was conferred without an increased risk of adverse events as relative to intravenous immune globulin therapy. These findings suggest an effective role of corticosteroids in treating Kawasaki disease as an initial therapy strategy among high-risk patients."

POTENTIAL IMPACT: There are several validity and applicability concerns with this study. Most are inherent to the process of combining studies with different methodologies and study definitions. A longer duration of illness before therapy was associated with an increased risk of coronary anomalies highlighting the need for early diagnosis and intervention. There was a significant reduction in coronary aneurysms when corticosteroids were used in conjunction with IVIG and Aspirin as initial therapy for Kawasaki disease. The reduction was most pronounced in those a high risk of IVIG resistance. It appears prudent to strongly consider the adjunctive use of corticosteroids in those at high risk. It remains unclear if the same benefit exists in those not at high risk for IVIG resistance. There was no benefit of using corticosteroids a rescue therapy indicating that if corticosteroids are to be used they should be used as initial therapy.

SURGERY

1. Appendicitis: Biomarkers: Acad Emerg Med. 2011
2. Appendicitis: CT with PO Contrast Utility: Ann Surg. 2014
3. Appendicitis: Early Analgesia: Pediatrics. 2005
4. Appendicitis: Morphine: Ann Emerg Med. 2007
5. Appendicitis: MRI: Pediatr Radiol. 2012
6. Appendicitis: Non-Operative (Adults): JAMA. 2015
7. Appendicitis: Non-Operative Meta-Analysis: Peds. 2017
8. Appendicitis: PAS Derivation: J Pediatr Surg. 2002
9. Appendicitis: PAS Validation: J Pediatr. 2008
10. Appendicitis: PAS Adolescent Females: Acad EM. 2016
11. Appendicitis: PAS and Ultrasound: J Pediatr. 2015
12. Appendicitis: Point of Care Ultrasound: Acad EM. 2014
13. Appendicitis: Radiology Ultrasound: Acad EM. 2013
14. Appendicitis: Risk Calculator Derivation: Pediatrics 2018
15. Appendicitis: Time to Appendectomy: J EM. 2015

16. Appendicitis: Time to Appendectomy: JAMA Peds 2017
17. Intussusception: 3 View XRAY (Retro): PEC 2007
18. Intussusception: 3 View XRAY (Prospective): PEC 2012
19. Intussusception: Exam and XRAY: Am J EM. 2012
20. Intussusception: Point of Care Ultrasound: Ann EM. 2012
21. Intussusception: POCUS Meta-Analysis Amer J EM 2019

APPENDICITIS: BIOMARKER TESTING

In children 3-18 years of age who present to an emergency department with acute abdominal pain and suspected appendicitis are novel biomarkers (Interleukin-6,Interleukin-8) when compared to traditional biomarkers (White blood cell count, Absolute neutrophil count and C-reactive protein) accurate in distinguishing those with and without appendicitis?

Janienne Kondrich, M.D., Adriana Manikian, M.D.

July 2011

Kharbanda AB, Cosme Y, Liu K, Spitalnik SL, Dayan PS.

DISCRIMINATIVE ACCURACY OF NOVEL AND TRADITIONAL BIOMARKERS IN CHILDREN WITH SUSPECTED APPENDICITIS ADJUSTED FOR DURATION

Acad Emerg Med. 2011 Jun;18(6):567-74.
PubMed ID: 21676053

STUDY DEFINITIONS	
POPULATION	Inclusion: 3-18 years, present to ED with acute abdominal pain for < 96 hours, evaluated for possible appendicitis (treating physician obtained blood tests, CT and/or ultrasound, or surgical consultation to diagnose appendicitis) Exclusion: Pregnancy, prior abdominal surgery, chronic gastrointestinal illness (cystic fibrosis, inflammatory bowel disease, sickle cell anemia, chronic pancreatitis, diabetes, immunosuppression), medical condition limiting ability to obtain accurate history (e.g., substantial language or developmental delay), CT or ultrasound of abdomen performed prior to ED arrival, abdominal trauma in past 7 days Setting: Single Children's Hospital ED, 8/2008-11/2009
TESTS	White blood cell count with automated differential Absolute neutrophil count C-reactive protein Interleukin-6 Interleukin-8
REFERENCE STANDARD	Presence or absence of appendicitis 1. Operative patients: Pathologist histopathology report, perforated appendix was determined from surgeon's postoperative note. 2. Non-operative patients: Follow-up telephone at 14 to 21 days. If the family could not be reached, a review of the hospital electronic record was conducted
OUTCOME	Area under the receiver operating characteristics curve (AUC) Test characteristics at optimal cutoff point Stratified by duration of pain (< 24, 24-48, and > 48 hours) and by appendicitis status (perforated appendicitis, non-perforated appendicitis, or no appendicitis).
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. The diagnosis of appendicitis in a patient with abdominal pain is often difficult and time-sensitive, given both non-specific symptoms and the possibility of perforation in untreated appendicitis.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. There were several reference standards used. The presence or absence of appendicitis for those who had an appendectomy was determined by the histopathology report written by an attending pathologist. A perforated appendix was determined by the attending surgeon's post-operative note. Those who did not undergo an appendectomy were followed up by telephone and if unavailable by hospital medical record review.
Were those interpreting the test and reference standard blind to the other results?	The study laboratory technicians who analyzed the study serum for IL-6, IL-8 and CRP levels were blinded to the patient's final diagnosis. The authors do not explicitly state whether the pathologists and surgeons determining the reference standard were blinded, but it can likely be assumed that the IL-6 and IL-8 levels were not known or were not yet available to these physicians. WBC, ANC, and CRP levels were reported in the same hospital system in which they worked and could easily be accessed by the pathologist. The treating surgeons were mostly likely aware of these values for their patients. It is unlikely that knowledge of these laboratory results would affect the interpretation of what is observed intraoperatively or on histopathologic examination.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	No. Only patients in whom appendicitis was strongly suspected were taken for an appendectomy. It would have been unethical to submit all patients to the risk of possibly unnecessary surgery.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 280, 33% with AP of which 23% perforated
N = 259 complete serum samples

See Clinical Bottom Line for Test Characteristic Table

BEST TEST FOR EACH TIME INTERVAL

TIME	TEST	CUTOFF	AUC	LR (+)
24 hours	IL-6	> 11.3	0.78	2.6
24-48 hours	CRP	> 20.8	0.89	6.6
> 48 hours	WBC	> 10	0.92	3.8

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	IL-6 and IL-8 levels are currently not available at most medical centers. The test characteristics provided were stratified as to duration of pain, which can be difficult to accurately assess clinically. The kappa statistic provided for interrater agreement on duration of pain was 0.63. Further, even if the test results are likely reproducible the test characteristics do not accurately distinguish the presence of appendicitis.
Are the study results applicable to the patients in my practice?	Since the study was conducted in another pediatric emergency department in NYC with similar demographics, the study results are likely applicable to our patients. However, the authors did not provide a table of study patient characteristics. The severity of disease can affect test characteristic (spectrum) bias. Those with severe disease (e.g. perforation with abscess) may have a higher sensitivity likelihood ratio of a positive test.
Will the test results change my management strategy?	No. The test characteristics for the lab tests currently available (CBC, CRP) are not sufficiently accurate to change practice. In addition, the presence of other inflammatory conditions (pelvic inflammatory disease, colitis) may increase false positives.
Will patients be better off as a result of the test?	This article contributes to the growing body of research on novel biomarkers. A reliable biomarker for diagnosing appendicitis would benefit patients. There will be decreased CTs and thus radiation exposure, and perhaps also time from arrival to ED to OR, possibly reducing the risk of perforation. However, at this time, patients will not be better off as a result of the biomarkers proposed in this study, as neither the traditional nor the novel biomarkers demonstrated great diagnostic ability.

CLINICAL BOTTOM LINE

BACKGROUND: The diagnosis of appendicitis in children and adolescents is difficult. The classic presentation of umbilical pain that moves to the right lower quadrant, with anorexia, vomiting and fever, is less common in practice than in textbooks, particularly in the early stages of illness and with younger children. The identification of a biomarker that are diagnostic of appendicitis, with sufficient sensitivity and specificity, would be of great benefit. The primary imaging modalities used currently for the diagnosis of appendicitis, CT of the abdomen and pelvis with contrast and RLQ ultrasound, have their own limitations.

CLINICAL QUESTION: In children 3-18 years of age who present to an emergency department with acute abdominal pain and suspected appendicitis are novel biomarkers (Interleukin-6, Interleukin-8) when compared to traditional biomarkers (White blood cell count, Absolute neutrophil count and C reactive protein) accurate in distinguishing those with and without appendicitis?

DESIGN/RISK OF BIAS: This was a prospective cohort study of both traditional and new biomarkers as diagnostic tools in patients who underwent evaluation for possible appendicitis. In this pilot study, the authors explored the diagnostic accuracy of these five biomarkers as a function of the duration of abdominal pain and appendicitis status (no appendicitis, non-perforated appendicitis and perforate appendicitis).

It would have been interesting to see how the biomarkers performed in conjunction with the others, and perhaps, in future studies, in conjunction with physical examination and inconclusive findings on ultrasound. It would also had been helpful to provide a more detailed description of patient's characteristics for those with and without appendicitis

PRIMARY RESULTS: The study enrolled 280 patients of which 33% had appendicitis. Of those with appendicitis 23% had a perforated appendix. All biomarkers studies were higher in those with appendicitis and even higher in those with a perforated appendix. In patients without appendicitis biomarkers are initially low and decreased further over time. In patients with either non-perforated or perforated appendicitis, biomarker levels rise and reach maximum values at different time intervals.

BEST TEST AT EACH TIME INTERVAL						
Time (hrs)	Test	Cutoff	AUC (95% CI)	LR (+)	Sensitivity	Specificity
24	IL-6	> 11.3	0.78 (0.71, 0.86)	2.6	82.1% (69, 91%)	68.5% (58, 78%)
24-48	CRP	> 20.8	0.89 (0.81, 0.97)	6.6	87% (65, 97%)	86.8% (71, 95%)
> 48	WBC	> 10	0.92 (0.84, 0.99)	3.8	100% (70, 100%)	73.3% (58, 85%)

APPLICABILITY: This is a pilot study. IL-6 and IL-8 levels are currently not available at most medical centers. The test characteristics provided were stratified as to duration of pain, which can be difficult to accurately assess clinically. The kappa statistic provided for inter-rater agreement on duration of pain was 0.63 which represents a "good" level of agreement beyond chance.

AUTHOR'S CONCLUSION: "Although interleuken-6, the white blood cell count, the absolute neutrophil count, and C-reactive protein are all increased in patients with appendicitis, levels of these markers fluctuate over the course of illness. Serum interleuken-6 is a potentially useful novel biomarker for patients with suspected appendicitis. Duration of symptoms may be an important variable to consider when interpreting laboratory values in patients with acute abdominal pain."

POTENTIAL IMPACT: This study provides a basis for further research into the use of biomarkers in the diagnosis of appendicitis. The results alone, however, are not be sufficient to change practice. It is unlikely that any one laboratory test would adequately predict appendicitis with sufficient sensitivity to result in few missed cases and sufficient specificity to result in a low negative laparotomy rate acceptable to our pediatric surgery colleagues. New biomarkers, may however improve the accuracy of clinical decision instruments such as the pediatric appendicitis score in conjunction with ultrasound results.

APPENDICITIS:
CT ENTERAL CONTRAST UTILITY

In adult patients with suspected appendicitis undergoing evaluation by abdominal CT and non-elective appendectomy what is the diagnostic accuracy of CT with intravenous contrast alone compared to CT with intravenous and enteral (oral and/or rectal) contrast compared to a reference standard of intraoperative and pathology findings in distinguishing between those with and without appendicitis?

Dana Suozzo, M.D., Joanne Agnant, M.D.
February 2015

Drake FT, Alfonso R, Bhargava P, Cuevas C, Dighe MK, Florence MG, Johnson MG, Jurkovich GJ, Steele SR, Symons RG, Thirlby RC, Flum DR; Writing Group for SCOAP-CERTAIN

ENTERAL CONTRAST IN THE COMPUTED TOMOGRAPHY DIAGNOSIS OF APPENDICITIS

Ann Surg. 2014 Aug;260(2):311-6.
PubMed ID: 24598250

STUDY DEFINITIONS	
POPULATION	Inclusion: >18 years, non-elective appendectomy undergoing CT imaging Exclusion: None Setting: 56 hospitals in Washington State. Enrollment period not specified
TEST A	CT with IV contrast only
TEST B	CT with IV contrast and enteral contrast (oral and/or rectal)
REFERENCE STANDARD	Intraoperative and pathology reports abstracted from the medical record
OUTCOMES	Primary Outcome: Accuracy of final radiology interpretations and final pathology report Secondary Outcomes: Time to operating room Cost consideration Side effects: Nausea Risks: Aspiration during anesthesia
DESIGN	Observational: Prospective and retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. Patients were those with suspected appendicitis who underwent CT scan and operative evaluation and appendectomy. The authors used propensity scoring in attempt to eliminate bias from confounding characteristics. Table 1 compares patient characteristics. Patients were similar except for time from ED admit to OR and perforation rate. There were more perforations in the IV plus enteral contrast group (17.4%) compared to IV contrast alone group (14.7%). Since it is easier to identify appendicitis if a perforation this could bias the study results in favor of the IV plus enteral contrast group. In the regression analysis, there proved to be no difference in the study results when adjusting for this difference.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. Intraoperative and pathology findings were abstracted from the medical record.
Were those interpreting the test and reference standard blind to the other results?	No. Surgeons were not blinded to the patient's clinical findings or CT results. It is however, unlikely that knowledge of these would have biased the pathology findings and. It is unclear but likely that radiologists had access to at least some of the patient's clinical data. This may have influence the interpretation of the CT scan.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	Yes. This study only included those patients with suspected appendicitis undergoing CT imaging and elective appendectomy

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 6,401
Intravenous only = 4,191
Enteral = 2,210 (Oral = 2,137, Rectal = 52, Oral and Rectal = 22)

CONCORDANCE (ACCURACY)	
Intravenous only	90.4%
Intravenous and Enteral	90.0%
Enteral only	92.6%
No Contrast	85.7%

Odds ratio = (Intravenous + Enteral) / (Intravenous only)
Unadjusted Odds Ratio: 0.63, 95% CI (0.05, 0.79)
Adjusted* Odds Ratio: 0.95, 95% CI (0.72, 1.25)
*Adjusted for, age, sex, weight, comorbidity, hospital type and perforation

There was no difference in concordance based on hospital location (rural versus urban) of by presence of a surgical or other residencies.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	Unclear. This study took place in 56 hospitals. It is unclear if both radiology faculty and residents were interpreting the CT's or why a specific contrast regimen was used at an institution. Whether the choice of contrast regimen was a result of hospital specific protocol or influenced by patient characteristics. In additional there was no attempt to determine inter-rater reliability of CT scan interpretation, which may be influence by a variety of factors.
Are the study results applicable to the patient in my practice?	Not necessarily. Although patient's age 18-24 years old were included in the study, we did not know how ill they were at initial presentation, and the majority were healthy without comorbidities. The inclusion of multiple hospitals in a variety of setting adds to the studies generalizability.
Will the results change my management strategy?	Possibly. This would require a collaborative effort between emergency medicine, surgery and radiology.
Will patients be better off as a result of the test?	Possibly. The time spent in the ED (50 minutes less) and costs were decreased in patients imaged with IV contrast only. Patient comfort and satisfaction were not evaluated. Without oral or contrast, it is difficult to assess for alternative diagnoses such as bowel obstructions and colitis.

CLINICAL BOTTOM LINE

BACKGROUND: Appendicitis is the most common surgical emergency with a population life-time risk of approximately 7-8%. CT imaging with contrast has decreased to the time to diagnosis, decreased the negative laparotomy rate and identified alternative diagnosis. New CT's with enhanced imaging may not require the enteral contrast that was used with prior CT's.

CLINICAL QUESTION: In adult patients with suspected appendicitis undergoing evaluation by abdominal CT and non-elective appendectomy what is the diagnostic accuracy of CT with intravenous contrast alone compared to CT with intravenous and enteral (oral and/or rectal) contrast compared to a reference standard of intraoperative and pathology findings in distinguishing between those with and without appendicitis?

DESIGN/VALIDITY: This was a well-designed study with some of the limitations inherent to use of large databases though this was an exclusive surgical database with data from 56 hospitals in a variety of settings in Washington State. The study included 6,401 patients (4,191 Intravenous only and 2,210 Enteral (2,137 Oral, 52 Rectal and 22 both oral and rectal). Patients were those with suspected appendicitis who underwent CT scan and operative evaluation for appendectomy. This population may represent selection bias and may not be comparable to all patients with suspected appendicitis.

PRIMARY OUTCOME: The authors present the concordance of CT and intraoperative findings. Concordance (accuracy) is a weighted average of sensitivity and specificity. In a situation, such as appendicitis when a high sensitivity is preferred over specificity it would have been helpful to present and compare other test characteristics of the contrast regimens such as sensitivity, specificity, predictive values and likelihood ratios. Propensity scoring and was used to adjust for potential confounding variables. Logistic regression was used to determine the independent effects of predictor variables. In the primary analysis, the concordance of CT and intraoperative findings was nearly identical: in the CT with Intravenous contrast only group (90.4%) and the CT with Intravenous and enteral contrast group (90.0%) with an adjusted odds ratio (Intravenous + enteral/intravenous only) of 0.95 95%CI (0.72, 1.25). This is a neither a clinical or a statistically significant difference. The ED length of stay was approximately 50 minutes less in the Intravenous only group. Patient specific outcomes such a pain scores, vomiting rate and overall satisfaction were not studied.

APPLICABILITY: The study's results are enhanced by the inclusion of many study hospitals in a variety of settings. The study results may not be generalizable to all adults with suspected appendicitis or to children. Specific clinical circumstances which necessitated an evaluation for appendicitis were not available in the study database.

AUTHOR'S CONCLUSION: "Data from SCOAP-CERTAIN suggest that enteral contrast does not offer diagnostic benefit for patients who undergo appendectomy. Furthermore, within each category of hospital type, CT scans enhanced only with IV contrast performed as well as CT scans in which enteral contrast was also used, suggesting that these findings are broadly generalizable. Increased ED efficiency, patient comfort, and safety may be improved without compromising diagnostic effectiveness. Enteral contrast should be eliminated in IV-enhanced CT scans performed for suspected appendicitis."

POTENTIAL IMPACT: The use of CT with Intravenous contrast can decrease the likelihood of bowel related alternative diagnoses such as colitis and bowel obstruction. This article should result in discussions with radiology and surgery colleagues to see if enteral contrast can be eliminated in settings with new generation scanners. Without enteral contrast, it is difficult identify alternative diagnoses such as bowel obstructions and colitis.

APPENDICITIS:
EARLY ANALGESIA

In pediatric patients presenting to the emergency department with acute abdominal pain suspicious of appendicitis does the administration of Morphine when compared to Placebo increase the proportion of patients with a delayed diagnosis of appendicitis, a missed appendicitis or a perforated appendicitis?

Michael Mojica, M.D.
July 2017

Green R, Bulloch B, Kabani A, Hancock BJ, Tenenbein M.

EARLY ANALGESIA FOR CHILDREN
WITH ACUTE ABDOMINAL PAIN.

Pediatrics. 2005 Oct;116(4):978-83.
PubMed ID: 16199711

STUDY DEFINITIONS	
POPULATION	Inclusion: 5-16 years, non-traumatic abdominal pain, within 48-hours of onset, surgical consultation warranted for a possible surgical condition by pediatric emergency medicine faculty Exclusion: Allergy to opiates, opiate use within 4 hours, hypotension, absence of a parent. Setting: Single Children's Hospital ED (Canada), 2/2000-3/2002
INTERVENTION	Morphine Sulfate 0.05 mg/kg (maximum dose of 10 mg)
CONTROL	Normal Saline (Placebo): An equivalent volume
CO-INTERVENTIONS	Assessment Form: Completed by emergency physician at baseline and 15 minutes after the intervention and by the surgeon or senior surgical resident (≥ PGY-4) within 1 hour of study intervention 1. Clinical signs and symptoms: Location of the pain, abdominal tenderness, guarding, psoas, obturator, and Rovsing signs, pain with jumping. 2. Degree of confidence in diagnosis before labs and imaging: 0% to 100%, Pain Assessment: Validated color analog scale at baseline and 15 minutes after the intervention, repeated if subsequent doses were needed. Ongoing Pain: The same dose of study medication was repeated at the emergency physician's discretion. If pain persisted after 2 doses of study medication, additional analgesia at the surgeon's discretion. Monitoring: Oxygen saturation and vital signs recorded every 10 minutes. Follow-up: Admitted patients were monitored. Discharged patients had telephone follow-up within 2 weeks. Operating room and pathology reports were reviewed for laparotomy patients
OUTCOME	Primary Outcome: Rate of missed appendicitis Secondary Outcomes: 1. Perforated appendicitis rate 2. Change in pain score 3. Pediatric emergency physician's confidence of in the diagnosis. 4. Pediatric surgeons or surgical resident's confidence in the diagnoses.
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Randomization was performed in blocks of 10 by the hospital pharmacy.
Was randomization concealed?	Yes. The pharmacy prepared identical syringes of Morphine Sulfate and Normal Saline solution. While not explicitly stated it appears that there was not an opportunity to bias the randomization process.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. See Table 1. There was no statistically significant difference between the 2 study groups in median pain score, RLQ tenderness, positive Rovsing, psoas or obturator signs or voluntary or involuntary guarding and time from study intervention to surgical assessment.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Patients, parents, nurse and emergency medicine and surgical providers were blinded to the study group. Patients were blinded to their initial color analog scale pain scores.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	All discharged patients received a phone follow up from a study nurse within two weeks. The proportion of patients reached for follow up was not presented.
Were patients analyzed in the groups to which they were randomized?	Though not explicitly stated, it appears that all patients were analyzed in the group to which they were randomized (intention to treat analysis).
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 108 (Morphine 52, Placebo 56)

ED DISPOSITION			
	OPERATION	ADMIT/OBSERVED	DISCHARGED
MORPHINE	25/52 (48.1%)	19/52 (36.5%)	8/52 (15.4%)
PLACEBO	24/56 (42.9%)	22/56 (39.3%)	10/56 (17.9%)

OUTCOME	MORPHINE	PLACEBO
APPENDICITIS	31/52 (59.6%)	26/56 (46.4%)
MISSED APPENDICITIS	0/52 (0%)	1/56 (1.8%)
NEGATIVE LAPAROTOMY	1/52 (1.9%)	4/56 (7.1%)

Perforation: In the text is states that “Perforated appendicitis occurred in 27 patients with no difference between groups.” In Table 2 it appears as if all patients with appendicitis were perforated.

Pain Score Reduction
Morphine: 2.2 cm
Placebo: 1.2 cm
Mean Difference: 1.0 cm, P = 0.015
In general, a 1.5 cm reduction is considered clinically significant.

ED MD ASSESSMENT OF CHANGE IN PAIN			
	BETTER	WORSE	SAME
MORPHINE	88.5%	0%	11.5%
PLACEBO	63.5%	0%	44.2%

MD CONFIDENCE IN THE DIAGNOSIS			
	PreRx	PostRx	RISK DIFFERENCE (95% CI)
MORPHINE	68.9%	69.5%	1.2% (-2.9, 5.3%)
PLACEBO	65.5%	70.9%	5.3% (2.7, 7.9%)

Surgeon Confidence in Diagnosis
Morphine: 73.8%
Placebo: 73.6%
Risk Difference: 0.01%, 95% CI (-0.39, 0.4%)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence intervals were presented only for the “confidence” outcomes (see above) and were fairly wide given the small sample size.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Patients presented to a single Children's hospital ED. The high rate of appendicitis and perforated appendicitis likely indicate that this is a referred population rather than a population that presents primarily to the emergency department.
Were all patient important outcomes considered?	Yes. The outcomes typically associated with appendicitis were included. In addition to change in pain score it would have been helpful to assess patient or parent satisfaction with the study interventions.
Are the likely treatment benefits worth the potential harm and costs?	There was a statistically significant decrease in pain scores in those that received Morphine. There was no increase in poor appendicitis outcomes or an increase in adverse outcomes associated with Morphine.

CLINICAL BOTTOM LINE

BACKGROUND: At the time of this study, the use of opiates for pediatric patients with abdominal pain was controversial. The concern for the use of opiates was based on the possibility of masking a surgical condition. The proponents of opiates believe they will alleviate only non-surgical pain and improve the sensitivity of physical exam via relaxation of abdominal musculature. The literature seems to support the use of opiates in adult patients with abdominal pain. Unfortunately, the data in pediatrics has not been as conclusive.

CLINICAL QUESTION: In pediatric patients presenting to the emergency department with acute abdominal pain suspicious of appendicitis does the administration of Morphine when compared to Placebo increase the proportion of patients with a delayed diagnosis of appendicitis, a missed appendicitis or a perforated appendicitis?

DESIGN/VALIDITY: This was a well-designed, placebo controlled, blinded randomized clinical trial that included 108 patients in the primary analysis. Patients were randomized to receive 0.05 mg/kg of Morphine Sulfate (maximum of 10 mg) or an equivalent volume of Normal Saline placebo. It may be argued that this is a lower dose than the 0.1 mg/kg typically recommended and therefore less likely to show a difference compared to placebo. Inclusion was based on the emergency physicians concern for a surgical condition. 100% of patients had right lower quadrant tenderness. There was no pain cutoff for study inclusion though the mean pain scores were moderate (Morphine group: 6.65, 95% CI (6.27, 7.03), Placebo group: 6.66, 955 CI (6.29, 7.02)) and a high proportion of patients had signs of peritonitis (e.g. guarding) or appendicitis specific signs (e.g. Obturator sign).

PRIMARY RESULTS: There was no statistically significant difference in the appendicitis outcomes of perforation, missed appendicitis or negative laparotomy between the Morphine and Placebo groups. There was a clinically significant reduction in pain score in the Morphine group (2.2 cm) but not in the Placebo group (1.2 cm). The difference in reduction in pain score (1.0 cm) between the two groups was statistically significant. In general, a 1.5 cm difference in a visual analog pain scale is considered clinically significant. Morphine did not change the emergency physician's confidence in the diagnosis and there was no difference in the surgeon confidence comparing the Morphine and Placebo groups.

APPLICABILITY: The study's results are likely generalizable to emergency department patients who meet the studies inclusion and exclusion criteria. 53% of enrolled patients had appendicitis and 47% of patients with appendicitis had a perforated appendicitis. These rates seem somewhat high. The high rate of appendicitis and perforated appendicitis likely indicate that this a referred population rather than a population that presents primarily to the emergency department. The applicability to populations with a higher or lower prevalence of disease is unclear.

AUTHOR'S CONCLUSION: "Our data showed that morphine effectively reduced the intensity of pain among children with acute abdominal pain, and it seems that morphine does not mask the physical signs of acute appendicitis. A multicenter trial to study this issue in more depth may be warranted."

POTENTIAL IMPACT: There was a statistically significant reduction in pain after administration of Morphine. The reduction in pain was significantly more that the Placebo group. However, there were no differences in disposition from the emergency department, no increase in poor appendicitis outcomes (missed or perforated appendicitis or negative laparotomy) or increases in adverse events associated with Morphine use.

APPENDICITIS:
MORPHINE ANALGESIA

In children with suspected appendicitis does the administration of Morphine prior to surgical consultation when compared to Placebo result in a decrease in pain or a delay in the time to a surgical disposition decision?

Eric Weinberg M.D., Dennis Heon M.D.
October 2007

Bailey B, Bergeron S, Gravel J, Bussières JF, Bensoussan A.

EFFICACY AND IMPACT OF INTRAVENOUS MORPHINE BEFORE CONSULTATION IN CHILDREN WITH RIGHT LOWER QUADRANT PAIN SUGGESTIVE OF APPENDICITIS: A RANDOMIZED CLINICAL TRIAL.

Ann Emerg Med. 2007 Oct;50(4):371-8.
PubMed ID: 17597256

STUDY DEFINITIONS	
POPULATION	Inclusion: 8-18 years, RLQ abdominal pain ≤ 3 days, pain score ≥ 5/10 cm, Presumed appendicitis ≥ 2 of: migration periumbilical to RLQ pain, vomiting, fever > 38°C (100.4°F) orally, RLQ tenderness or guarding, Rovsing's or psoas sign. Need for surgical consultation Exclusion: Ultrasound/CT confirmed appendicitis prior to surgical assessment, prior analgesia other than Acetaminophen or Ibuprofen, hemodynamically unstable, sepsis, immunocompromised, patients with a history of: sickle cell anemia, abdominal surgery, inflammatory bowel disease, pancreatic or biliary disease, allergy to Morphine, suspected or confirmed pregnancy. Setting: Single Children's Hospital ED (Canada), 2/2004-6/2006
INTERVENTION	Morphine: 0.1 mg/kg (maximum dose of 5 mg) intravenously over 20 minutes
CONTROL	Placebo (similar-looking and same volume) intravenously over 20 minutes
OUTCOME	Primary Outcomes: 1. Difference in pain (visual analog scale) at baseline and 30 minutes 2. Time between arrival and surgery consultant disposition decision Secondary outcomes: Proportion of: perforated appendicitis, unnecessary laparotomy or laparoscopy, missed diagnoses, admission for observation Hospital length of stay Effect of the intervention on: probability of appendicitis, physical examination
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized to receive 0.1 mg/kg Morphine (maximum 5 mg) infusion or a similar looking Normal Saline infusion over 20 minutes. Computer-generated block randomization with blocks of variable size was performed.
Was randomization concealed?	Yes. A randomization list was drawn up by a statistician and given directly to the pharmacy. Pharmacists then dispensed Morphine or Normal Saline with same volume in same vials. Doctors accurately guessed the identity of the study drug approximately 50% of the time.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Groups were similar in the factors presented in Table 1. In addition, the proportion with appendicitis who underwent appendectomy was the same (Morphine 88% vs Placebo 91%).
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	All personnel and patients were blinded to the group assignment until study completion.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Unclear. There was no mention of the procedure for follow up of patients discharged or admitted without an appendectomy though the primary outcomes were assessed during the ED stay. One patient in the placebo group was discharged and then readmitted with an abdominal abscess.
Were patients analyzed in the groups to which they were randomized?	Yes. An intention-to-treat approach was used for the primary analysis. 3/45 (7%) of patients in the placebo group withdrew from the study by parents due to inadequate analgesia.
Was the trial stopped early?	Yes. Initial sample size determination required 184 patients. Interim analysis at 90 patients. “Because the delay was lower in the Morphine group compared with the Placebo by 34 minutes, we thought it was unlikely that another 90 patients would have a 90-minute difference in favor of the placebo group” A 1-hour different was considered to be the minimal clinically significant difference. Ultimately enrolled 90 patients.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 90
Appendicitis (%): Morphine 64%, Placebo 69%

Primary Outcome 1: Decrease in Pain Score
Morphine group: 24 (± 23) mm decrease in VAS
Placebo group: 20 (± 10) mm decrease in VAS.
Mean difference: 24 – 20 = 4 mm, 95% CI (-5,12)
(Authors clinically significant difference: 13 mm)

Primary Outcome 2: Time: ED to Surgical Disposition
Morphine: Median 269 minutes, 95% CI (240, 355 min)
Placebo: Median 307 minutes, 95% CI (239, 415 min)
Median Difference: 34 minutes, 95% CI (-105, 40 min)
(Authors clinically significant difference: 1 hour)

Secondary Outcomes (Table 2)
No clinically significant difference in proportion of: perforated appendicitis, unnecessary surgery, missed diagnosis, duration of admission or probability of appendicitis

No difference in proportion who lost rebound or guarding.
In patients who did not have appendicitis, there was a difference in the proportion of patients who lost rebound tenderness (Morphine 64%% vs. Placebo: 0%).
In patients who did have appendicitis, there was no difference in the proportion of patients who lost rebound tenderness (Morphine 12% vs. Placebo 17%).

Adverse Events: Morphine group 1 patient each with: itching, vomiting, drowsiness and nausea with dizziness

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

For the primary outcomes, there was no clinically (> 13 mm for VAS score, > 60 minutes for time interval) or statistically significant difference (95% confidence intervals include 0).

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. Patients were 8-18-year-old at a tertiary care urban pediatric center with RLQ pain. Their group of suspected appendicitis patients had a 64% rate of appendicitis which is somewhat high.
Were all patient important outcomes considered?	Yes. Although the outcome of “time to surgical decision” may be influenced by many factors not related to analgesia and physical examination findings.
Are the likely treatment benefits worth the potential harm and costs?	Unclear. This study found no difference in the primary outcomes of change in pain score and time to surgical decision making. There was no difference in rates of perforated appendicitis, missed appendicitis, and negative laparotomy between the two groups. This seems to support the safety of Morphine administration. However, the change in pain score was the same in both groups questioning the efficacy of Morphine. There was a 9% rate of side events in the Morphine group compared to 0% in the placebo group. These were minor (itch, vomiting, diarrhea, drowsiness) but could be stressful to the patient and their family.

CLINICAL BOTTOM LINE

BACKGROUND: The use of opiates for patients with abdominal pain is controversial. The theory against the use of opiates is based on the fear of masking a surgical condition. The proponents of opiates believe they will alleviate only non-surgical pain, in addition to improving the sensitivity of physical exam via relaxation of abdominal musculature. Multiple past studies have been performed to address these theories. The literature seems to support the use of opiates in adult patients with abdominal pain. Unfortunately, the data in pediatrics has not been as conclusive. Prior to this study there were two randomized clinical trials evaluating the efficacy of opiates in pediatric patients with surgical abdominal pain. One study found no increase in the rates of misdiagnosis or perforated appendicitis, and the other study showed an increase in the specificity of physical exam after Morphine was administered.

CLINICAL QUESTION: In children with suspected appendicitis does the administration of morphine prior to surgical consultation when compared to placebo result in a decrease in pain or a delay in the time to a surgical disposition decision?

DESIGN/VALIDITY: This study attempts to add to the body of evidence by analyzing the efficacy of morphine compared to placebo in children ages 8-18 years with RLQ pain requiring a surgical consult. It was a well-designed randomized clinical trial that included 87 patients in the primary intention to treat analysis. The major limiting factor in this study is small sample size leading to limited power.

PRIMARY OUTCOME: Morphine successfully reduced pain in this population (24 ± 23) mm decrease on a visual analog pain scale (VAS)). However, placebo also reduced pain to a similar degree (20 ± 10) mm decrease in VAS. There was no clinical or statistically significant difference between the two groups (Mean difference: 24 – 20 = 4, 95% CI (-5,12 mm). There was no clinically or statistically significant difference in the time interval from ED arrival to surgical disposition decision between the two groups (Morphine group: 269, 95% CI (240, 355 min), Placebo group: 307, 95% CI (239, 415 min), Median Difference = 269 – 307 = -38, 95% CI (-105, 40) minutes. In addition, there was no significant difference in proportion of: perforated appendicitis, unnecessary surgery, missed diagnosis, duration of admission, probability of appendicitis, those who lost rebound or guarding.

APPLICABILITY: The study's results are likely generalizable to the majority of ED settings. However, the patient population had an approximately 65% prevalence of appendicitis. This may be lower in setting where imaging is obtained prior to surgical consultation.

AUTHOR'S CONCLUSION: "This trial adds to the existing evidence that analgesia in children with acute abdominal pain, and in particular those with appendicitis, does not appear to impair diagnostic accuracy. In the future, a large multicenter study should evaluate adverse events such as perforated appendicitis."

POTENTIAL IMPACT: This study demonstrates that the use of Morphine does not influence physical examination findings or the time from ED arrival to surgical disposition decision. 7% of the Morphine group had mild adverse events. It is unclear if these adverse events required intervention. However, the efficacy of Morphine in patients with suspected appendicitis is left in doubt. Both Morphine and Placebo resulted in a clinically significant difference in pain. However, there was a non-significant difference in improvement in pain between the two treatment groups. Further study is required to assess Morphine's efficacy in this condition. The decision to provide analgesia will require collaboration between ED providers and surgical consultants.

APPENDICITIS:
MRI

In pediatric patients with suspected appendicitis what are the test characteristics of MRI of the abdomen and pelvis without contrast?

Maria Lame, M.D., Karen Goodman M.D
May 2014

Moore MM, Gustas CN, Choudhary AK, Methratta ST, Hulse MA, Geeting G, Eggli KD, Boal DK.

MRI FOR CLINICALLY SUSPECTED PEDIATRIC APPENDICITIS: AN IMPLEMENTED PROGRAM.

Pediatr Radiol. 2012 Sep;42(9):1056-63.
PubMed: 22677910

STUDY DEFINITIONS	
POPULATION	Inclusion: 5-17 years old, clinically suspected appendicitis in the ED setting Exclusion: Not provided Setting: Single children's hospital, 3/2010-3/2011
INTERVENTION	MRI of the abdomen and pelvis without IV/PO contrast and without sedation. Breath holding technique for > 8 years and respiratory triggering technique < 8 yrs
CONTROL	Intraoperative findings and pathological diagnosis or clinical follow-up
OUTCOME	Diagnostic test characteristics of MRI, timing parameters
DESIGN	Observational: Retrospective cohort study

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. Patients were in the ED or hospitalized with clinical "suspicion" of appendicitis requiring imaging for further evaluation.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The reference standard was intraoperative findings and pathological diagnosis or clinical follow-up.
Were those interpreting the test and reference standard blind to the other results?	Yes. Scans were read within one hour of completion so those reading the MRI were blinded to the final diagnosis. Though it is not explicitly stated it is likely that the MRI results were utilized by the surgeons to determine the need for operative intervention. It is also unclear if pathologists and clinical outcome assessors were blind to the MRI result. It is unlikely that the lack of blinding in these cases could influence the interpretation of the outcomes.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	No. It would have been unethical to bring every patient to the operating room. Clinical follow up was used as a surrogate measure. All true-positive, false-positive and the false-negative cases were confirmed by pathology. The true negatives were confirmed by clinical follow up. The number available for clinical follow up was not provided

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

		APPENDICITIS		
		YES	NO	
MRI	POSITIVE	40	5	45
	NEGATIVE	1	162	163
		41	167	208

Prevalence (Appendicitis): 41/208 = 19.7%
Sensitivity: 40/41 = 97.6%, 95% CI (87.1, 99.9%)
Specificity: 162/167 = 97.0%, 95% CI (93.2, 99.0%)
Predictive Value (+) Test: 40/45 = 88.9%, 95% CI (76.0, 96.3%)
Predictive Value (-) Test: 162/163 = 99.4%, 95% CI (96.6, 99.9%)
Likelihood Ratio (+) Test: (40/41) / (5/167) = 32, 95% CI (13.7, 77.4).
Likelihood Ratio (-) Test: (1/41) /(162/167) = 0.024, 95% CI (0.004, 0.174)

TIME PARAMETERS	
Request to first sequence	78.7 ± 52.5 min
First to last sequence	14.2 ± 8.8 min
Last sequence to report	57.4 ± 35.2 min
Request to preliminary report	150.3 ± 65.4 min
Preliminary to final report	316.5 min ± 407.7 min

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Unclear. The radiologists were board certified pediatric radiologists. It would have been helpful to have a kappa statistic as a measure of inter-rater reliability.
Are the study results applicable to the patients in my practice?	No. The patient description was limited to an age range and gender. No other demographic characteristics were reported. There were no set criteria for referral for MRI. 20% of the patients had a perforated appendicitis. This could increase the sensitivity of MRI (spectrum bias).
Will the test results change my management strategy?	A change in management strategy would require collaboration between Pediatric emergency medicine, surgery and radiology. The availability of MRI is the factor limiting its application. Ideally, it would have been helpful to measure the test performance of MRI in the population with suspected appendicitis with an equivocal ultrasound.
Will patients be better off as a result of the test?	Benefits to the patient are less exposure to radiation, reduced risk of contrast reactions and the identification of alternative diagnoses.

CLINICAL BOTTOM LINE

BACKGROUND: Pediatric patients who present to the ED with a clinical picture suggestive of appendicitis represent a diagnostic dilemma. Currently, ultrasound is the initial imaging study of choice for pediatric patients with suspected appendicitis. However, the appendix may not be visualized in a large proportion of patients with ultrasound and the test characteristics are user dependent. In patients with a high pretest probability of appendicitis and an equivocal ultrasound, CT or observation may be required. CT scanning entails a risk due to radiation exposure and potential contrast reactions.

CLINICAL QUESTION: In pediatric patients with suspected appendicitis what are the test characteristics of MRI of the abdomen and pelvis without contrast?

DESIGN/RISK OF BIAS: The study included 208 patients with appendicitis 41 (19.7%) of which had appendicitis. This was a well-designed study though there are a number validity concerns that may limit its applicability.

1. There were no set criteria for patient selection. The exclusion criteria and the demographic characteristics of those suspected to have appendicitis were not provided. The imaging decision was left to the discretion of the treating clinical team. This could create a potential for selection bias
2. Existing pediatric clinical decision rules for appendicitis were not used for risk stratification prior to imaging.
3. A pediatric radiologist read the MRI but interrater reliability was not measured.
4. The criteria for a negative MRI were: a normal appendix visualized (36%) or an appendix was not visualized but there were no signs of accompanying inflammation. In 2/3 of the patients the appendix was not visualized.
5. A perforation rate of 20% in the study population entails a risk of spectrum bias. It could be easier to identify appendicitis by MRI in a population with a high rate of abscess than in a population without perforation. This could potentially increase the reported sensitivity.

PRIMARY RESULTS: Investigators found that the MRI was highly specific (97%, 95% CI (87.1, 99.9%)) and sensitive (97.6%, 95% CI (87.1, 99.9%)) for appendicitis. The small sample size however results in unacceptable performance at the lower limits of the confidence intervals. The negative predictive value was 99.4%, 95% CI (96.6, 99.9%) with positive predictive value of 88.9%, 95% CI (76.0, 96.3%). The average time to completion of the study was 14 minutes and 78 minutes to get the study started once it was ordered. However, the time from request to final report was 7.8 hours.

APPLICABILITY: The patient description was limited to an age range and gender. No other demographic characteristics were reported. There were no set clinical criteria for referral for MRI possibly resulting in selection bias. In addition, 20% of the patients had a perforated appendicitis. This could increase the sensitivity of MRI (spectrum bias).

AUTHOR'S CONCLUSION: "Our clinical implementation demonstrates that MRI without contrast agent is an effective and efficient method of imaging children with clinically suspected appendicitis. Using an expedited four-sequence protocol, sensitivity and specificity are comparable to CT while avoiding the detrimental effects of ionizing radiation."

POTENTIAL IMPACT: While the study results are promising, the many potential biases discussed above limit the applicability of MRI of the abdomen and pelvis without contrast for pediatric patients with suspected appendicitis now. A change in management strategy would require collaboration between pediatric emergency medicine, surgery and radiology. The availability of MRI is the factor limiting its application. Ideally, it would have been most helpful to measure the test performance of MRI in the population with suspected appendicitis and an equivocal ultrasound.

APPENDICITIS:
NONOPERATIVE MANAGEMENT (ADULTS)

In adult patients with uncomplicated appendicitis on CT scan, is antibiotic treatment non-inferior to surgical management for an outcome of treatment efficacy defined in the operative group as successful appendectomy and in the antibiotic group as not requiring an appendectomy within 1 year?

Michael Mojica, M.D.
October 2016

Salminen P, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, Tuominen R, Hurme S, Virtanen J, Mecklin JP, Sand J, Jartti A, Rinta-Kiikka I, Grönroos JM.

ANTIBIOTIC THERAPY VERSUS APPENDECTOMY FOR TREATMENT OF UNCOMPLICATED ACUTE APPENDICITIS: THE APPAC RANDOMIZED CLINICAL TRIAL

JAMA. 2015 Jun 16;313(23):2340-8.
PubMed ID: 26080338

STUDY DEFINITIONS	
POPULATION	Inclusion: 18-60 years with uncomplicated appendicitis (AP) on CT scan Exclusion: Complicated AP on CT (appendicolith, perforation, abscess) CT contraindications: Pregnant, lactating, contrast or iodine allergy, renal insufficiency Additional: Metformin use, Peritonitis (not defined), Serious systemic illness (not defined) Setting: Multicenter (n=6) Finland, 11/09-6/12
INTERVENTION (ABX GROUP)	Inpatient: IV Ertapenum 1 gram QD x 3 days (first dose in ED) followed by Outpatient: PO Levofloxacin 500 mg QD + Metronidazole 500 mg TID x 7 days
CONTROL (OR GROUP)	Appendectomy: Open laparotomy 94.5%, Laparoscopic 5.5% Pre-operative antibiotics (1st does in ED) Post-operative antibiotics only if wound infection
OUTCOME	Primary: Treatment Efficacy Antibiotic group: Rate of resolution of AP: Discharge without need for surgical intervention and no recurrent appendicitis within a 1 year follow up period Operative group: Rate of successful appendectomy Secondary: Adverse Events Post-operative complications: wound infection within 30 days, incisional hernia, bowel obstruction, chronic abdominal pain including incisional pain Length of stay Duration of sick leave required Follow-up pain scores Adverse effects of antibiotics Pneumonia
DESIGN	Interventional: Randomized clinical trial (non-inferiority hypothesis)

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized using a closed envelope method.
Was randomization concealed?	Likely Yes though not explicitly stated. Used opaque envelopes. Of 4,400 patients who underwent appendectomy during the study period only 1, 379 assessed for study eligibility. Opportunity for selection bias.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. See Table 2, similar with respect to factors listed. May have been helpful to include a comparison of vital signs as a measure of acuity.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The study was open label (not blinded). The objectivity of the primary outcomes suggest that lack of blinding would not affect the primary outcomes
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDY'S CONCLUSION?	
Was follow-up complete?	<u>Operative Group</u> Primary outcome. Yes 100% since outcome was successful appendectomy assessed at time of admission Secondary outcome. No 21% (58/272) loss to follow up. This may underestimate the risk of post op complications. <u>Antibiotics group</u> Primary outcome and secondary outcomes. 11.7% (30/256) lost to follow up but still included in the primary analysis because review of district records did not reveal an appendectomy. This requires the assumption that no one had an appendectomy out of their district.
Were patients analyzed in the groups to which they were randomized?	Yes. The primary analysis was an intention to treat analysis (See figure). A per protocol analysis with those in the Antibiotic group who underwent surgery on the initial visit analyzed in the Operative group was not completed.
Was the trial stopped early?	Yes. The trial was stopped early due to poor enrollment. Only 528 of the 550 patients suggested by their power analysis were included in the primary analysis.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Primary Outcome: Treatment efficacy

Operative Group:
Successful appendectomy = 99.6% (272/273) 95% CI (98-100%)
(1 improved prior to OR)

Antibiotic Group:
Not requiring appendectomy within 1 year = 72.7% (186/256), 95% CI 66.8-78.0%)

Risk Difference (ARD)
= Risk Antibiotic group – Risk Operative group = 72.7% - 99.6% = - 27%, 95% CI (-31.6%, (+) infinity)

Alternatively, 27.5% (70/256) did require appendectomy (6% during the initial hospitalization and 21% subsequently)

If a per protocol analysis was conducted and the 15 patients in the Antibiotic group who underwent appendectomy at the initial visit were analyzed in the operative group then the delayed appendectomy rate is 22.8% (55/241). No patients with a delayed appendectomy had a complicated appendicitis

Secondary Outcomes: Adverse events
Surgical complication rate (absolute risk)
Antibiotic group (All) = 2.8% (1-6%)
Antibiotic group (Underwent delayed appendectomy) = 7.0%, 95% CI (2.0, 17%),
Operative group = 20.5%, 95% CI (15.3, 26.4%)

Risk Difference (Operative – Antibiotics): 20.5 – 2.8 = 17.7%, 95% CI (11.9, 23.4%)
Risk Difference (Operative – Antibiotics with delayed appendectomy): 20.5 – 7.0 = 13.4%, 95% CI (4.9, 21.9%)

Operative group:
2 with incisional hernia (1 required repair)
1 require laparoscopic adhesiolysis,
23 chronic abdominal complaints
Sick leave time 19 vs 7 days
Lower initial length of stay

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The lower limit of the confidence interval of – 31.6% is lower than the pre-specified non-inferiority margin of - 24% proposed by the authors. Therefore, cannot conclude that Antibiotics is non-inferior to Operative management. The non-inferiority margin is somewhat arbitrary but based on the evidence that was available.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. Table 2. In addition, the complicated appendicitis rate on initial CT of 24% (337/1379) is similar to US studies. Co-morbid conditions were not reported but they may have been excluded under “serious systemic illness”
Were all patient important outcomes considered?	Did not include a cost analysis. Stated that they measured antibiotic adverse events but did not report them.
Are the likely treatment benefits worth the potential harm and costs?	Potential benefits include that nearly ¾ of patients in the ABx group did not require an operation within 1 year However, ¼ required a second hospital admission. None of the patient who needed a subsequent appendectomy had a complicated appendicitis. In the US. a repeat diagnosis of appendicitis who likely entail another CT scan. The potential for the development of antibiotic resistance with broad spectrum antibiotics should be considered.

CLINICAL BOTTOM LINE

BACKGROUND: Prior to the antibiotic era, appendicitis resulted in significant pelvic infections. Early appendectomy was found to significantly decrease this risk. Recently the use of antibiotics as primary therapy for appendicitis has been explored. A systematic review of 5 randomized clinical trials was conducted and demonstrated that approximately 75% of those receiving antibiotics were cured within two weeks and without major complications (including recurrence) within one year (Wilms, Cochrane 2011, PubMed ID: 22071846). However, the lower 95% CI was 15.2% below the 20% non-inferiority margin for the primary outcome resulting in an inconclusive outcome. In addition, the trails were assessed as being of poor to moderate quality.

CLINICAL QUESTION: In adult patients with uncomplicated appendicitis on CT scan is antibiotic treatment non-inferior to surgical management for an outcome of treatment efficacy defined in the operative group as successful appendectomy and in the antibiotic group as not requiring an appendectomy within 1 year?

DESIGN/VALIDITY: This was a well-designed, multicenter (6 institutions in Finland), open label, that included 528 patients in the primary intention-to-treat analysis. Uncomplicated appendicitis was defined as the absence of appendiceal perforation, abscess or appendicolith. In the surgery group, approximately 95% of patients underwent an open appendectomy. This could potentially increase the post-operative complication rate compared to laparoscopic appendectomy. In addition, the trial was stopped early due to poor enrollment. Only 528 of the 550 patients suggested by their power analysis were included in the primary analysis. In addition, 30 (11%) of the patients in the antibiotic group was lost to follow up but were included in the primary analysis based on review of hospital district records.

PRIMARY OUTCOME: For the primary outcome of treatment efficacy, 99.6% (272/273) 95% CI (98-100%) of the patients in the operative group underwent a successful appendectomy. In the antibiotic group, 72.7%, 95% CI (66.8-78.0%) did not requiring an appendectomy within 1 year. No patients who underwent a delayed appendectomy had a complicated appendicitis. The absolute risk difference for the primary outcome is = -27% (72.7% - 99.6%) with a 95% CI (-31.6% to (+) infinity). The lower limit of the CI of – 31.6% is lower than the non-inferiority margin of - 24% proposed by the authors. Therefore, it cannot be concluded that antibiotics are non-inferior to operative management. The complication rate in the operative group was higher in the operative group including when compared to patients in the antibiotic group who underwent appendectomy.

APPLICABILITY: The study is applicable to adult patients with uncomplicated appendicitis on CT scan who do not meet exclusion criteria. The surgical complication rate would likely be lower in a U.S. population primarily undergoing laparoscopic appendectomy.

AUTHORS CONCLUSION: “Among patients with CT-proven, uncomplicated appendicitis, antibiotic treatment did not meet the pre-specified criterion for non-inferiority compared with appendectomy. Most patients randomized to antibiotic treatment for uncomplicated appendicitis did not require appendectomy during the 1-year follow-up period, and those who required appendectomy did not experience significant complications.”

POTENTIAL IMPACT: This paper may not change the current operative approach to appendicitis but it presents an opportunity to re-evaluate this approach with our surgical colleagues. If an antibiotic only approach is considered it is a perfect opportunity for shared decision making with the patient and the surgeon.

APPENDICITIS:
NON-OPERATIVE MANAGEMENT: META-ANALYSIS

In pediatric patients with uncomplicated appendicitis that is managed non-operatively (antibiotics without appendectomy) when compared to appendectomy what is the efficacy defined as discharge from the hospital without an appendectomy and safety defined as complications or recurrence of appendicitis?

Guillermo De Angulo, M.D., MSc., Michael Mojica, M.D.

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Georgiou R, Eaton S, Stanton MP, Pierro A, Hall NJ.

EFFICACY AND SAFETY OF NON-OPERATIVE TREATMENT FOR ACUTE APPENDICITIS: A META-ANALYSIS

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STUDY DEFINITIONS	
POPULATION	Inclusion: Patient: < 18 years of age, acute uncomplicated appendicitis. Studies: Any study design (retrospective, prospective, RCT). English language Exclusion: Patient: Complicated appendicitis: perforated appendicitis, ruptured appendicitis, appendicitis with abscess, appendiceal mass, appendicitis in children with malignancy Studies: Included adults and children, Setting: Japan (3), U.S. (2), Others (5), Published 2007-2015.
INTERVENTION	Non-operative treatment with antibiotics
CONTROL	6/10 studies had a control group of appendectomy 4/10 studies did not have a control group
OUTCOME	Primary Outcome: Short term efficacy: Discharge from initial hospitalization without appendectomy Secondary Outcomes: 1. Complications: As defined by the individual studies (not including recurrence) 2. Long term efficacy: A. Recurrent of appendicitis: Biopsy confirmed or received an additional course of non-operative therapy by end of follow-up period B. Underwent an appendectomy by end of follow-up period 3. Length of hospital stay: Initial admission 4. Length of hospital stay: Initial admission and additional stay for recurrence
DESIGN	Systematic review and meta-analysis: Multiple study designs

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review explicitly address a sensible clinical question?	Yes. The question is the efficacy and safety of non-operative therapy for uncomplicated appendicitis. However, studies had different: techniques to diagnose appendicitis, antibiotics utilized, duration of follow-up and criteria to select eligible patients (randomized (1), inclusion criteria (4), parent selection of treatment (5)).
Was the search for relevant studies detailed and exhaustive?	Yes. The authors searched the Cochrane Central Register of Controlled Trials, Medline, and EM Base. Search terminology was provided in a supplement. They also searched the reference list of included studies. The search was limited to English and unpublished data was excluded. There was no assessment reported for the possibility of publication bias.
Was the risk of bias of the primary studies assessed?	Yes. See Table 1. For the single randomized trial a Jadad score was used to assess the risk of bias. The study had a score of 3 out of 5. 2 points were deducted for lack of blinding. The methodological index for non-randomized studies (MINORS) was used to assess the risk of bias of observational studies (n=9). MINORS has a maximum score of 24 for comparative studies and 16 for non-comparative studies. For the 5 comparative studies the scores were 13, 16, 16, 20 and 22 out of 24. For the 4 non-comparative studies the scores were: 7, 9, 10, and 12 out of 16.
Were the selection and assessment of studies reproducible?	Unclear. Two independent researchers selected the studies with disagreements resolved by a third researcher. There was no measure of interrater reliability provided for either study inclusion or study quality.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

Yes. For the primary outcome. Heterogeneity of the study results was assessed using the I^2 statistic (I^2 > 30% considered heterogeneous). There was substantial heterogeneity for the recurrence outcome. Visual inspection of the Forrest plots (Figures 2-6) reveals substantial overlap in the study confidence intervals. This method of assessing heterogeneity may be biased by the large confidence intervals of smaller studies. A random effects model (more conservative) was used for the meta-analysis.

WHAT ARE THE OVERALL RESULTS OF THE REVIEW?

N = 10 studies:
1 RCT
5 comparative cohort studies and
4 cohort studies without a comparison group
Prospective (7), retrospective (3)

Efficacy Analysis: n= 413 (non-operative), 353 (operative)

<u>Efficacy: Short Term: No Appendectomy on Initial Admit</u>
97% (396/413), 95% CI (95.5, 98.7%)
Figure 2: n =10 studies
Low heterogeneity: I^2 = 0%, p = 0.7

<u>Long Term Efficacy: Recurrence of Appendicitis</u>
14% (68/396), 95% CI (7%, 21%)
Non-operative (n=19/68)
Appendectomy (n=49/68)
Figure 3: n =10 studies
Marked heterogeneity: I^2 = 80%, p < 0.001

<u>Long Term Efficacy: No Appendectomy</u>
82%, 95% CI (77, 87%).
Low heterogeneity: I^2 = 34%, p = 0.14

<u>Length of Stay: Initial Hospitalization</u>
Mean difference: 0.48 days, 95% CI (0.2, 0.8 days)
Operative < Non-Operative (Favors appendectomy)
N = 4 studies, Non-operative (n=151), Operative (n=189)
Marked heterogeneity: I^2 = 54 %, p = 0.002

<u>Length of Stay: Initial and Subsequent Hospitalization</u>
Mean difference: 1.1 days, 95% CI (-1.2, 3.5 days)
N = 2 studies, Non-operative (n=142), Operative (n=126)
High heterogeneity: I^2 = 93%, p = 0.0002

<u>Non-Recurrence Complications</u>:
Risk difference: 2%, 95% CI (0, 5%)
N = 5/6 of comparative studies
Low heterogeneity: I^2 = 0%, p = 0.47

DID THE REVIEW ADDRESS CONFIDENCE IN EFFECT ESTIMATES?

See confidence intervals for primary and secondary outcomes above.

OUTCOME	N	I^2	P
SHORT TERM EFFICACY	10	0%	0.69
RECURRENCE	10	80%	< 0.01
LONG TERM EFFICACY	10	34%	0.14

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were all patient-important outcomes considered?	The study assessed initial success rate, long term success rate, and complication rates. There was no analysis of cost, cost-effectiveness or patient and family quality of life (e.g. missed days from school or work). These are important outcomes that should be assessed in further studies.
Are any postulated subgroup effects credible?	The only subgroup analysis included was for length of stay in the 6 comparative studies. Data was available for 4 studies for initial length or stay and 2 studies for initial and subsequent length of stay. The clinical significance of the differences seen is unclear.
What is the overall quality of the evidence?	The overall quality of the evidence is poor. The differences in study methodology and the heterogeneity of many of the outcomes likely should have ended the study as a systematic review and not progressed to a meta-analysis.
Are the benefits worth the costs and potential risks?	The benefit of avoiding an operation and its potential complications should be weighed against the potential for recurrence. It is not clear that this study adequately answers these questions. Future randomized clinical trials are needed to better answer these questions.

CLINICAL BOTTOM LINE

BACKGROUND: Acute appendicitis is one of the most common surgical emergencies and has been traditionally treated with appendectomy. There is a limited though growing literature that antibiotics without surgery may be an effective alternative to appendectomy for patients with uncomplicated appendicitis. Non-surgical treatment of appendicitis may be an appealing alternative to some families.

CLINICAL QUESTION: In pediatric patients with uncomplicated appendicitis that is managed non-operatively (antibiotics without appendectomy) when compared to appendectomy what is the efficacy defined as discharge from the hospital without an appendectomy and safety defined as complications or recurrence of appendicitis?

DESIGN/RISK OF BIAS: This was a systematic review and meta-analysis to determine the efficacy and safety of non-operative treatment for acute uncomplicated appendicitis in children. The primary short term efficacy outcome of not requiring an appendectomy during the initial admission included 413 non operative patients and 353 who underwent an appendectomy.

10 studies were included: 1 randomized clinical trial, 5 cohort studies comparing non operative treatment to appendectomy and 4 cohort studies without a comparison group. Seven of the studies were prospective and 3 were retrospective. Studies methodology differed in the techniques to diagnose appendicitis, antibiotics utilized, criteria to select eligible patients (randomized (1), inclusion criteria (4), parent selection of treatment group (5)) and duration of follow up for non-operative patients. Given the variability in methodology and the substantial heterogeneity of some of the outcomes it is not clear that these studies should have been combined in a meta-analysis.

PRIMARY RESULTS: Overall non-operative treatment of acute uncomplicated appendicitis was successful in 97%, 95% CI (95.5, 98.7%) of children during the initial hospital episode. The adjusted incidence of recurrent appendicitis was 14%, 95% CI (7, 21%). The long-term efficacy (not undergoing an appendectomy), determined at the final reported follow up period, was 82%, 95% CI (77, 87%). In the comparative studies the initial hospital stay was shorter by a mean of 0.5 days, 95% CI (0.2, 0.8 days) though hospital stay including the follow up period was similar in the non-operative treatment and appendectomy groups. There was no difference in the rate of complications. There was no analysis of cost, or patient and family quality of life (e.g. missed days from school or work).

APPLICABILITY: The lack of randomized control studies in the meta-analysis and the variability of the individual study's methodology make it difficult to generalize the study's results to a specific population or intervention (e.g. antibiotic selection). Furthermore, there was no presentation of inter-rater reliability for study inclusion or quality.

AUTHOR'S CONCLUSION: "This study has provided a comprehensive review of the existing literature pertaining to non-operative therapy for acute, uncomplicated appendicitis in children. As far as we are aware, it is the first such review to synthesize data specifically from children.

The study highlights the lack of robust evidence comparing non-operative therapy with appendectomy in children but provides data the support and justify ongoing and future endeavors to assimilate such evidence so that we can best serve the huge number of children who develop appendicitis every year. This review also confirms a position of equipoise between treatment approaches in such trials.

Until such studies are completed, we would recommend that non-operative therapy of children with acute, uncomplicated appendicitis be reserved for those participating in carefully designed research studies."

POTENTIAL IMPACT: Two quotes for the from the author's discussion nicely describe the study's potential impact. "Although it is tempting to draw conclusions regarding comparative efficacy from our comparative analysis of non-operative therapy and appendectomy, we consider that to do so would be misleading because of the nature of the underlying studies." "We therefore caution against the use of these data as definitive comparative evidence and await future randomized studies."

This study likely should have ended as a systematic review and not progressed to a meta-analysis. There is a need for more randomized controlled trials in the pediatric population to assess the efficacy and safety of non-operative treatment of acute uncomplicated appendicitis compared to appendectomy. The authors suggest that their study may serve as a basis for establishing clinical equipoise for further randomized, controlled trials.

APPENDICITIS:
PEDIATRIC APPENDICITIS SCORE DERIVATION

In pediatric patients with abdominal pain suggestive of appendicitis do history, physical examination and laboratory tests accurately identify those with and without appendicitis?

Michael Mojica, M.D.
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Samuel M.

PEDIATRIC APPENDICITIS SCORE

J Pediatr Surg. 2002 Jun;37(6):877-81.
PubMed ID: 12037754

STUDY DEFINITIONS	
POPULATION	Inclusion: 4-15 years, abdominal pain suggestive of acute appendicitis Exclusion: Appendicular mass with periappendiceal abscess Setting: 2 Hospitals (England), Enrollment dates not specified. Published 2002, Methods state “in the last 5 years”
RULE PARAMETERS	Prospective data collection form 1. Demographic data: Age, sex 2. History of symptom duration: Anorexia, nausea, vomiting, migration of pain from the periumbilical area to the right lower quadrant (RLQ) 3. Physical examination findings: Right iliac fossa tenderness to palpation, RLQ tenderness to hopping, cough/percussion RLQ tenderness, fever 4. Laboratory: Total WBC, differential, urinalysis.
REFERENCE STANDARD	Pathology report 1. Inflamed: Mucosal only 2. Suppurative: Mucosal necrosis with transmural extension 3. Perforated: Mucosal necrosis with transmural extension with peritonitis 4. Gangrenous: Not defined Clinical follow up: Method not specified
OUTCOME	Rule Characteristics
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. The potential predictors included: demographic data, history of symptoms, physical examination findings and laboratory findings. These are the predictors most commonly associated with the risk of appendicitis.
Were all important predictors present in significant proportion of the study population?	Unclear. The proportion of patients with each of the predictors was not presented.
Were the outcome event and predictors clearly defined?	Yes and No. The outcome of appendicitis was clearly defined and categorized based on pathology. 34% of the patients did undergo appendectomy. The follow up method for these patients was not described. Physical examination predictors were not defined. Cutoffs for continuous predictors (fever, WBC count, ANC) were not provided.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Temporally, the assessment of the predictors occurred prior to the assessment of the outcome. It is likely that those assessing the predictors were involved in the patient’s operative management. However, knowledge of the predictors should not affect the pathologists report.
Was the sample size adequate (including an adequate number of outcome events)?	In general, for logistic regression, 10 outcome variables are required for each of the predictors. This study identified 8 predictors and would require 80 patients with appendicitis by this standard. 734 patients with appendicitis and 436 patients without appendicitis were included.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? How precise was this measurement? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

N = 1,170
Appendicitis: 734/1,170 (63%),
No Appendicitis: 436/1,170 (37%)

INFLAMED	35%
SUPPURATIVE	36%
PERFORATED*	20%
GANGRENOUS*	9%
*29% perforated or gangrenous	

Negative Laparotomy Rate:
36/1,170 (3%) without appendicitis went to the OR

Pediatric Appendicitis Score (PAS):
8 independent predictors of appendicitis identified
(See Table in the results section of the Clinical Bottom Line)

Mean PAS score Appendicitis: 9.1 +/- 0.1
Mean PAS score No Appendicitis: 3.1 +/- 1.1

Sensitivity: 100% (CI not presented)
Specificity: 92% (8% negative laparotomy rate)
Predictive Value of a Negative Rule: 99%
Predictive Value of a Positive Rule: 96%

CUTOFF	MISSED APPENDICITIS	NEGATIVE LAPAROTOMY
5	0%	1.6%
6	0.7%	1.1%

≤ 5 not compatible with the diagnosis of appendicitis
≥ 6 compatible with the diagnosis of appendicitis (7-10 = high probability)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

Unclear. The proportion of patients with each score, rule characteristics at each cutoff off point were not provided so this could not be calculated.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

Yes. 66 additional children were assessed using the PAS after study completion
Rule Characteristics were similar to the derivation set.
Confidence intervals were not presented and are not calculable with the data provided.

	DERIVATION	VALIDATION
Sensitivity	100%	100%
Specificity	92%	87%
Predictive Value (+) Rule	96%	90%
Predictive Value (-) Rule	99%	100%

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

At what level of development is this rule? How can it be applied?	☐ I ☐ II ☐ III ■ IV This is a level IV clinical decision rule. A level IV rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. A Level IV rule requires further validation before it can be applied clinically.
Does the rule make clinical sense?	Yes, the parameters that make up the rule do make clinical sense. The variables in the rules are mostly objective.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. Patient history and laboratory findings are reproducible. Physical examination findings are open to interpretation and inter-rater reliability was not assessed.
Is the rule applicable to the patients in my practice?	Unclear. Little demographic data was presented. The study population had a 63% rate of appendicitis of which 29% were perforated or gangrenous. This is high compared to much of the appendicitis literature. This raises the possibility of spectrum bias. For example, patients with more severe illness have a greater likelihood of physical exam findings and higher laboratory values. This could result in a higher sensitivity when compared to populations with less severe disease.
Will the rule results change my management strategy?	No. This is the derivation of a clinical decision rule and requires further validation. However, the identified predictors are those that are currently used to assess the likelihood or appendicitis.
What are the benefits of applying the rule to my patients?	The benefits of applying the rule is that it allows for risk stratification. Patients with a very high PAS score could potentially go to laparotomy without the need for imaging. Patients with a very low score could be discharged with close follow up and return precautions. Patients with an intermediate score could be observed as an inpatient or imaging could be done for further risk stratification.
What are the risks of applying the rule to my patients?	The primary risk is missing a small number of patients with appendicitis with an increase in risk of complications.

CLINICAL BOTTOM LINE

BACKGROUND: The identification of which pediatric patients with abdominal pain have appendicitis is difficult. There are a number of clinical and laboratory factors that can be used to identify the risk of appendicitis. Unfortunately, no single predictor has been identified that has a high enough sensitivity to identify those with appendicitis in order to prevent a delay in diagnosis and complication such as perforation and a high enough specificity to prevent unnecessary surgery (negative laparotomy). A combination of factors may prove more accurate.

CLINICAL QUESTION: In pediatric patients with abdominal pain suggestive of appendicitis, do history, physical examination and laboratory tests accurately predict those at both low and high risk of appendicitis?

DESIGN/RISK OF BIAS: This was a prospective cohort study that included 1,170 patients in an attempt to identify independent predictors of appendicitis in children with abdominal pain. The aim was to derive and validate a clinical decision rule. There was no description of the method used to follow up on patients who did not undergo a laparotomy. It is unclear if these patients were discharged from or admitted for observation.

PRIMARY RESULTS: The study used logistic regression to identify independent predictors of appendicitis. 8 variables comprised the pediatric appendicitis score (range 0-10 points). Rule characteristics were: Sensitivity: 100%, Specificity: 92%, Predictive value of a Negative Test: 99% and Predictive value of a Positive Test: 96%. It is not specified at what rule score the rule characteristics apply to. Rule characteristics were similar in the internal validation set. 95% confidence intervals for the rule characteristics were not provided. In addition, a receiver operating characteristic curve with an area under the curve was not presented. Cutoff values for quantitative variables (Temperature, leukocytosis and polymorphonuclear neutrophilia were not presented).

The authors report that a PAS ≤ 5 is not compatible with the diagnosis of appendicitis while a PAS score ≥ 6 is compatible with the diagnosis of appendicitis and a score of 7-10 is associated with a high probability of appendicitis.

PEDIATRIC APPENDICITIS SCORE	POINTS
Anorexia	1
Nausea or vomiting	1
Migration of pain	1
Fever*	1
Tenderness over the right iliac fossa	2
Cough/percussion/hopping tenderness in the right lower quadrant	2
Leukocytosis*	1
Polymorphonuclear neutrophilia*	1
*The cutoffs for the continuous variables were not provided	

APPLICABILITY: It is unclear if this study's results can be generalized to other pediatric populations. Little demographic data was presented. The study population had a 63% rate of appendicitis of which 29% were perforated or gangrenous. This is high compared to much of the appendicitis literature. This raises possibility of spectrum bias. For example, patients with more severe illness have a greater likelihood of physical exam findings and higher laboratory values. This could result in a higher sensitivity when compared to populations with less severe disease. Inter-rater reliability of physical examination findings was not assessed and the reproducibility of some of the history parameters (anorexia, migration of pain) is questionable in young children

This is a level IV clinical decision rule. A level IV rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. Level IV rules require further validation before it can be applied clinically.

AUTHOR'S CONCLUSION: "Pediatric appendicitis score is a simple, relatively accurate diagnostic tool, which is applicable in all clinical situations and has been proposed as a guide to assist in deciding whether to operate or observe a child with abdominal pain. The scoring system can be used for repeated structured reevaluation during active observation."

POTENTIAL IMPACT: There are a number of concerns with the study's methodology. Patients with very low pediatric appendicitis scores can be managed non-operatively while those with very high score require a laparotomy. Patients with intermediate score can be admitted for serial assessments of exam findings. The authors acknowledge the difficulties in the diagnosis of appendicitis in children. "The Pediatric Appendicitis Score should be correlated with the clinical impression of the examiner because there always is an intangible ingredient in the diagnosis of appendicitis." Subsequent studies went on to validate the pediatric appendicitis score (Goldman, J Pediatr. 2008, PubMed ID: 18534219, Pogerelic, PEC 2015, PubMed ID: 25706925) and to integrate the pediatric appendicitis score with ultrasound imaging (Bachur, J Pediatrics, 2015, PubMed ID: 25708690).

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

APPENDICITIS:
PEDIATRIC APPENDICITIS SCORE VALIDATION

In pediatric patients with acute abdominal pain and suspected appendicitis does the application of the Pediatric Appendicitis Score accurately identify those with and without appendicitis?

Vaishali Shah, M.D., Adriana Manikian, M.D.
November 2014

Goldman RD, Carter S, Stephens D, Antoon R, Mounstephen W, Langer JC.

PROSPECTIVE VALIDATION OF THE PEDIATRIC APPENDICITIS SCORE

J Pediatr. 2008 Aug;153(2):278-82.
PubMed ID: 18534219

STUDY DEFINITIONS

POPULATION	Inclusion: 1-17 years of age, chief complaint of abdominal pain, < 7 days Exclusion: Prior diagnosis of appendicitis by imaging study, pain > 7 days Setting: Single Children's Hospital (Canada), 9/2003-3/2005
RULE PARAMETERS	Pediatric Appendicitis Score Parameters: 1. Anorexia 2. Nausea or vomiting 3. Migration of pain 4. Fever (>38 C or 100.4 F) 5. Tenderness over the right iliac fossa 6. Cough/percussion/hopping tenderness in the right lower quadrant 7. Leukocytosis (>10,000/ml^3) 8. Polymorphonuclear neutrophilia (>7,500/ml^3)
REFERENCE STANDARD	Inpatient records were reviewed for operative and pathology reports. Discharged patients had phone follow up.
OUTCOME	Rule characteristics
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?

Were the patients chosen in an unbiased fashion and do they represent a wide spectrum of severity of disease?	Unclear. Using the chief complaint of abdominal pain of less than 7 days they will have a wide spectrum of possible disease processes than for example patients with only right lower quadrant tenderness. The final diagnoses of those without appendicitis patients are not presented. It is also not clear which percentage of patients had mildly inflamed appendicitis, perforation, or gangrene. The rule characteristics are susceptible to spectrum bias. For example, it may be easier to identify a patient with an abscess than someone with an early distal tip appendicitis. Very limited demographic data are presented for those with and without appendicitis
Was there a blinded assessment of the criterion standard for all patients?	Unclear. It seems likely that surgeons were aware of the rule parameters before the operation. However, all patients with appendicitis were pathology proven. It is unlikely that pathologists were aware of the rule parameters.
Was there an explicit and accurate interpretation of the predictor variables and the actual rule without knowledge of the outcome?	Yes. The rule parameters were determined prior to the operation.
Was there 100% follow up of those enrolled?	849 were recruited and all were included in the primary analysis.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

N = 849, 139 (14.5%) with appendicitis

Mean PAS score
Appendicitis group: 7.0, SD 2.2
No appendicitis group: 1.9, SD 1.9
Mean Difference: 5.1, 95%CI (4.7, 5.5)

ROC Curve
The area under the receiver operating characteristic curve (AUC) was 0.948.
This indicates that the PAS score is highly accurate.

Score Performance

PAS	APPENDICITIS	NO APPENDICITIS
≤ 2	2.4%	97.6%
≥ 7	96%	4%

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

41% of the patient in the appendicitis group had a PAS of between 3-6. The authors suggest that these patients would need to undergo further imaging. With a cutoff of PAS ≥ 7 only 4% of patients without appendicitis would have undergone surgery. Conversely only 2.4% of patients with appendicitis with a PAS score of ≤ 2 would have been mistakenly discharged.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see Appendix)	☐ I ■ II ☐ III ☐ IV This is a level II clinical decision rule. Level II rules are validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. No impact analysis has been conducted. A level II rule can be used in a wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
Does the rule make clinical sense?	Yes. The parameters that make up the rule do make clinical sense. The variables in the rules are mostly objective.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	The interpretation of some of the rule components may be variable in young children. There was no attempt to determine inter-relater reliability for each component.
Is the rule applicable to the patients in my practice?	Unclear. Limited demographic parameters were provided. Likely generalizable to patients seen in other children's hospital pediatric ED's.
Will the rule results change my management strategy?	Use of the rule would require cooperation between ED physicians and pediatric surgeons. Use of the rule would result in a 4% negative laparotomy rate if patients with a PAS score when to the OR without imaging for confirmation. It is unclear if this would be acceptable to our surgeons.
What are the benefits of applying the rule to my patients?	The benefits of applying the rule is that it allows for risk stratification a PAS of greater than 7 would then save the patient radiation from a possible CT scan and save time undergoing evaluation in the ED because they would go to the OR. If they have a score < 2 the clinician can feel comfortable discharging the patient without undergoing imaging. Based on their results the benefits will apply to 40% of patients, which should decrease time to disposition, cost and adverse effects of radiation if the imaging modality is CT. This comes with minimal risk for missing appendicitis.
What are the risks of applying the rule to my patients?	The risks are missing the few patients with a low score who did have appendicitis (2.4% in this study). However, the amount of time and resources saved by using PAS scores of ≥ 7 or less than ≤ 2 could outweigh these risks.

CLINICAL BOTTOM LINE

BACKGROUND: There have been many attempts to derive an accurate method to determine which children with acute abdominal pain may have appendicitis. Samuel derived the accurate Pediatric Appendicitis Score (PAS) that included elements of the history, physical examination and basic laboratory testing that was internally validated (J Peds Surg, 2002, PubMed ID: 12037754). This study aimed to prospective validate the Pediatric Appendicitis score.

CLINICAL QUESTION: In pediatric patients with acute abdominal pain and suspected appendicitis does the application of the Pediatric Appendicitis Score accurately predict those with and without appendicitis?

DESIGN/RISK OF BIAS: This was a prospective cohort of 849 pediatric patients of which 139 (14.5%) had appendicitis There are some validity concerns in the study design. There is not an accurate description of the study population. In addition, there was no attempt to determine the inter-relater reliability of the each of the rule parameters and no planned subgroup analysis of older versus younger children

PRIMARY RESULTS: This study demonstrated that the PAS can be used with relatively high accuracy to stratify risk of having appendicitis in children 1-17 years of age who presented with acute abdominal pain of less than 7 days duration. The authors suggest risk stratification as follows: those with PAS ≤ 2 = low probability, 3-6 = moderate probability and ≥ 7 = high probability score.

A PAS of ≤ 2 had a 2.4% probability of appendicitis, while a PAS ≥ 7 had a 95% probability of appendicitis. In a significant number of patients with a PAS score of 3 to 6 (37% with appendicitis and 23% without appendicitis) the PAS was not accurate in ruling in or ruling out appendicitis, therefore these patients should undergo further observation or imaging.

PEDIATRIC APPENDICITIS SCORE	POINTS
Anorexia	1
Nausea or vomiting	1
Migration of pain	1
Fever (>38 C or 100.4 F)	1
Tenderness over the right iliac fossa	2
Cough/percussion/hopping tenderness in the right lower quadrant	2
Leukocytosis (>10,000/ml^3)	1
Polymorphonuclear neutrophilia (>7,500/ml^3)	1

APPLICABILITY: The interpretation of some of the rule components may be variable in young children. The study would have benefited from an assessment of inter-relater reliability for the physical examination parameters of the rule. Use of the rule would require cooperation between ED physicians and pediatric surgeons. Use of the rule would result in a 4% negative laparotomy rate if patients with a PAS score ≥ 7 were taken for laparotomy without confirmatory imaging. It is unclear if this would be acceptable to our surgeons.

This is a level II clinical decision rule. Level II rules are validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. No impact analysis has been conducted. A level II rule can be used in a wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve.

AUTHOR'S CONCLUSION: "The Pediatric Appendicitis Score is useful, because a value <2 (found in 73% of children without appendicitis) has high validity for ruling out appendicitis, and a score >7 (found in 61% of children with appendicitis) has a high validity for predicting the presence of appendicitis. Children with Pediatric Appendicitis Score of 3 to 6 (37% with appendicitis and 23% without appendicitis in this study) should undergo further investigation such as observation, ultrasonography, or computed tomography."

POTENTIAL IMPACT: 40% of children presenting with acute abdominal pain of less than 7 days' duration who have this rule applied would potentially benefit from decreased cost, time of evaluation, and radiation exposure. The next step in validation of the PAS score would be a larger, multicenter prospective study and an impact analysis assessment if the implementation of the rule can change clinical practice.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

APPENDICITIS:
PAS IN ADOLESCENT FEMALES

In females 13 to 21 years of age with suspected appendicitis, how accurate is the Pediatric Appendicitis Score in identifying appendicitis when compared to all other patients 3-12 years of age (female patients 3-12 years of age and male patients 3-21 years of age)?

Sheri-Ann Wynter, M.D., Joanne Agnant, M.D.
August 2016

Scheller RL, Depinet HE, Ho ML, Hornung RW, Reed JL.

UTILITY OF PEDIATRIC APPENDICITIS SCORE IN FEMALE ADOLESCENT PATIENTS.

Acad Emerg Med. 2016 May;23(5):610-5.
PubMed ID: 26824846

STUDY DEFINITIONS	
POPULATION	Inclusion: 3-21 years, RLQ abdominal pain or clinical concern for appendicitis by PEM Attending or Fellow Exclusion: Symptoms lasting longer 72 hours Pregnancy Referrals with imaging from an outside hospital Evaluation in the shock trauma suite for abdominal injury Underlying medical problems associated with recurrent abdominal pain Setting: Single, tertiary-care Pediatric ED, 11/2011- 6/2013
TEST/RULE	Pediatric Appendicitis Score (See Appendix))
REFERENCE STANDARD	Histologic pathology confirmed appendicitis at one month after the ED visit
OUTCOME	Rule characteristics
DESIGN	Observational: Retrospective cohort

ARE THE RESULTS VALID?	
Did participating patients present a diagnostic dilemma?	Yes. The study was done on patients who had right lower quadrant pain or clinically suspected appendicitis.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. Histologic pathology reports reviewed one month after the ED visit were used as the reference standard. Phone follow up of patients was not included. Patients with appendicitis who were seen at another hospital subsequently would not have been missed.
Were those interpreting the test and reference standard blind to the other results?	Attending physicians completed a paper-based questionnaire containing the clinical elements of the PAS at the time of the first physical examination and before the determination of the diagnosis. Two authors who were blinded to the PAS reviewed all pathology reports and consensus regarding positive histology was obtained.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	No. Histologic pathology reports were not present for all patients because not all patients underwent appendectomy. It is unethical to take all patients for an appendectomy to get a histologic pathology report. Furthermore, those that did not undergo appendectomy were considered to be without appendicitis for the purposes of this study).

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

ADOLESCENT FEMALES

	APPENDICITIS		
	YES	NO	
PAS ≥ 3 MODERATE/HIGH-RISK	42	208	250
PAS < 3 LOW RISK	1	21	22
	43	229	272

Prevalence: 43/272 = 15.8%
Sensitivity: 42/43 = 97.7%, 95% CI (87.9, 99.6%)
Specificity: 21/229 = 9.2%, 95% CI (5.4, 12.9%)
Predictive Value (+) Test: 42/250 = 16.8%, 95% CI (12.7, 21.9%)
Predictive Value (-) Test: 21/22 = 95.5%, 95% CI (78.2, 99.2%)
Likelihood Ratio (+) Test: (42/43)/(208/229) = 1.08 (1.01, 1.14)
Likelihood Ratio (-) Test = (1/42)/(21/229) = 0.25 (0.04, 1.84)

ALL OTHER PATIENTS

	APPENDICITIS		
	YES	NO	
PAS ≥ 3 MODERATE/HIGH-RISK	205	391	596
PAS < 3 LOW RISK	1	32	33
	206	423	629

Prevalence: 206/629 = 32.8%
Sensitivity: 205/206 = 99.5%, 95% CI (97.3, 99.9%)
Specificity: 32/423 = 7.6%, 95% CI (5, 10.2%)
Predictive Value (+) Test: 205/596 = 34.4%, 95% CI (30.7, 38.3%)
Predictive Value (-) Test: 32/33 = 97%, 95% CI (84.7, 99.5%)
Likelihood Ratio (+) Test: (205/206)/(391/423) = 1.08, 95% CI (1.05, 1.11)
Likelihood Ratio (-) Test: (1/206)/(32/423) = 0.06, 95% CI (0.01, 0.47)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	Unclear. There is no determination of inter-observer reliability on the PAS score. The is particularly important for the physical exam parameters that are open to interpretation.
Are the study results applicable to the patients in my practice?	Yes. We see adolescent females with RLQ pain who represent a diagnostic dilemma because they may have appendicitis or a gynecological reason for their pain such as ovarian torsion or pelvic inflammatory disease.
Will the results change my management strategy?	At a cutoff of > 3 sensitivities were similar, and at a cutoff of > 8, the specificity was better in adolescent females than in all other patients. This suggests that the PAS is a better test for applying to adolescent females at higher cut-offs. However, this may not preclude still pursuing gynecology diagnoses in parallel in adolescent females presenting with RLQ pain.
Will patients be better off as a result of the test?	Yes. At lower cut offs, such as PAS < 3, diagnostic testing may be reduced in adolescent female patients.

CLINICAL BOTTOM LINE

BACKGROUND: Adolescent females presenting to the ED with right lower quadrant abdominal pain present a diagnostic challenge. They are at risk for appendicitis as well as a variety of gynecologic pathologies. The Pediatric Appendicitis Score (PAS) has been shown in previous studies to perform better than other clinical prediction rules. It is clinically helpful for patient risk stratification into low, moderate, and high-risk categories for appendicitis, and the current general acceptance is that at a cutoff of less than 3, patients are low risk, and at a cutoff of higher than 8, patients are high-risk (See Appendix). However, it is not clear how well the PAS performs in the adolescent female subgroup. One prior study characterized the test characteristics of the PAS applied to the different sexes, but did not specify performance for different age groups.

CLINICAL QUESTION: In females 13 to 21 years of age with suspected appendicitis, how accurate is the Pediatric Appendicitis Score in identifying appendicitis when compared to all other patients 3-12 years of age (female patients 3 to 12 years of age and male patients 3-21 years of age)?

DESIGN/VALIDITY: This study is a retrospective, single-site, observational study that included 272 adolescent females and 689 other patients 3-21 years of age. Study investigators defined appendicitis as histologic pathology reports one month after ED presentation with a final interpretation of “appendicitis.” No appendicitis was defined as pathology reports with interpretations of “normal appendix,” “fecalith,” “fibrous obliteration” or “fecal plug,” as well as patients who did not undergo appendectomy at the study site. This may bias the study, as patients with appendicitis who sought care elsewhere may have been missed. This could have decreased the prevalence of appendicitis and decreased the sensitivity and negative predictive values presented in this study. However, this might have theoretically affected both the female adolescents and the all others group equally, so the effect may not be as important.

PRIMARY RESULTS: At a low-risk cutoff (PAS ≥ 3), there is no statistically significant difference in the sensitivity, specificity and negative predictive when female adolescents are compared to all other patients (SN 97.7% vs 99.5%, SP 9.2% v 7.6%, NPV= 95.5% vs 97%, respectively).

At a high-risk cutoff (PAS ≥ 7), there is no statistically significant difference in the specificity and negative predictive when female adolescents are compared to all other patients. (SP 72.9% v 65.5%, NPV= 90.3% vs 85.3%, respectively). There was however a statistically significant decrease in sensitively in adolescent females at this cutoff. (SN 58.1% vs 76.7%, respectively)

At a high risk cutoff (PAS ≥ 8), there is no statistically significant difference in the sensitivity and positive predictive when female adolescents are compared to all other patients. (SN 48.8% vs 55.8% 72.9% v 65.5%, PPV= 45.7% vs 55.8%, respectively). There was however a statistically significant increase in specificity in adolescent females at this cutoff. (SP 89%% vs 78.1%, respectively)

There was a statistically significant decrease in the positive predictive value for both a PAS score ≥ 3 (PPV 16.8% versus 34.4%), and a PAS score ≥ 7 (PPV 28.7% versus 52.2%) in adolescent females. This is likely due to the higher prevalence of alternative diagnoses in this population. A decrease in positive predictive value was not seen at a PAS cutoff of ≥ 8.

TEST CHARACTERISTICS		
	ADOLESCENT FEMALES	ALL OTHER PATIENTS*
Prevalence	15.8%	32.8%
Sensitivity	97.7%	99.5%
Specificity	9.2%	7.6%
Predictive Value (+) Test	16.8%	34.4%
Predictive Value (-) Test	95.5%	97%
Likelihood Ratio (+) Test	1.08	1.08
Likelihood Ratio (-) Test	0.25	0.06
*3-21 years		

RULE CHARACTERISTICS: ADOLESCENT FEMALES VERSUS ALL OTHERS				
Cutoff	SN	SP	PPV	NPV
≥ 3, < 3	NS	NS	Sig ↓	NS
≥ 7, < 7	Sig ↓	NS	Sig ↓	NS
≥ 8, < 8	NS	Sig↑	NS	Sig ↑
NS = no significant difference, Sig = significant difference ↑ Adolescent females > All others, ↓ Adolescent females < All others				

In is unclear why the authors did not assess interval likelihood ratios corresponding to the 3 most commonly used categories of the PAS particularly because the authors utilize the 3 risk categories in their Pediatric Appendicitis Pathway. A comparison of the area under receiver operating characteristic for the PAS may have been helpful. It may also may have been helpful to compare adolescent female to adolescent males and not include toddlers and children in the all other group.

APPLICABILITY: This study is largely generalizable to other ED populations, if the prevalence of appendicitis is similar (15.8% in female adolescents and 32.8% in all other patients). However, there is no determination of inter-observer reliability on the PAS score.

AUTHOR'S CONCLUSION: "Our study demonstrates that the Pediatric Appendicitis Score, as commonly used clinically (i.e., with cutoffs of 3 and 8), showed better specificity and equivalent sensitivity for female adolescent patients compared to all other patients, as well as a good negative predictive value in both groups. Overall, specificities in both groups were lower than has been reported in some previous literature, and positive predictive value was poor in all groups. This highlights the need for a physician to have a clear understanding of the score's use and limitations, especially with regard to age and sex. Further research is warranted to clarify this inter- action on a larger scale and assess a possible need for additional evaluation for patients in the high-risk group."

POTENTIAL IMPACT: Although there are some risks of bias concerns in this study, such as the classification of patients as negative for appendicitis whenever no pathology report existed, and the retrospective observational design, this is the first study to elucidate how well the PAS score performs in a problematic subpopulation.

In 2002, Samuel derived the Pediatric Appendicitis Score. (J Peds Surgery June 2002, PubMed ID: 12037754). Subsequent studies went on to validate the pediatric appendicitis score (Goldman, J Pediatr. 2008, PubMed ID: 18534219, Pogerelic, PEC 2015, PubMed ID: 25706925) and to integrate the pediatric appendicitis score with ultrasound imaging (Bachur, J Pediatrics, 2015, PubMed ID: 25708690).

APPENDIX: PEDIATRIC APPENDICITIS SCORE

PEDIATRIC APPENDICITIS SCORE	POINTS
Anorexia	1
Nausea or vomiting	1
Migration of pain	1
Fever (> 38 C)	1
Tenderness over the right iliac fossa	2
Cough/percussion/hopping tenderness in the RLQ	2
Leukocytosis (> 10,000/ml^3)	1
Polymorphonuclear neutrophilia (> 7,500/ml^3)	1

APPENDICITIS:
PEDIATRIC APPENDICITIS SCORE AND ULTRASOUND

In children with suspected appendicitis can a combination of radiologist performed ultrasonography (US) and the Pediatric Appendicitis Score (PAS) be used to adequately distinguish between those with and without appendicitis?

Maria Lame M.D., Inna Elikashvili D.O.
April 2015

Bachur RG, Callahan MJ, Monuteaux MC, Rangel SJ.

INTEGRATION OF ULTRASOUND FINDINGS AND A CLINICAL SCORE IN THE DIAGNOSTIC EVALUATION OF PEDIATRIC APPENDICITIS

J Pediatr. 2015 May;166(5):1134-9.
PubMed ID: 25708690

STUDY DEFINITIONS	
POPULATION	Inclusion: 3-18 with clinical suspected appendicitis requiring advanced imaging or a surgical consult. Of those that underwent both CT and US, only those that had US performed first were included Exclusion: Previous abdominal surgery, concurrent antibiotic use, chronic abdominal pain followed by specialist, chronic medical condition that would influence the presentation of appendicitis (systemic corticosteroid use, immunodeficiency, sickle cell, cystic fibrosis), cognitive disability that would interfere with communication or any advanced radiological imaging of the abdomen during the week before ED visit Setting: Single Children's Hospital ED, 4/2010-11/2012
TEST	Radiologist performed ultrasound: Positive: Report included: appendicitis, probable appendicitis, findings consistent with appendicitis, early appendicitis, evidence of perforation, phlegmon, or phlegmonous changes in the area of appendix, or "suspected perforation with abscess." If the final impression was not clear, evidence of a non-compressible dilated appendix or an appendicolith with secondary signs of appendicitis (e.g., echogenic fat, focal free fluid) also was considered a positive ultrasound. Negative: Report Included: normal appendix, no evidence of appendicitis, or normal ultrasound of the RLQ (with or without visualization of the appendix). When not specified in the final radiologist's impression, a visualized compressible appendix of normal caliber (< 7 mm diameter) also was considered negative. Reports indicating that the appendix was not visualized but there were no secondary signs of appendicitis also were considered negative. Equivocal: Reports not classified as positive or negative, Report summary included: equivocal ultrasound, non-diagnostic study, cannot exclude appendicitis, CT is recommended if clinical suspicions remains Report body included: nonvisualized appendix with possible secondary findings.
RULE	Pediatric Appendicitis Score (PAS): (See Appendix) Calculated retrospectively based on clinical findings recorded and CBC (WBC and differential)
REFERENCE STANDARD	Appendicitis: Pathology report Ruptured appendix: Intraoperative findings or cross sectional imaging indicating abscess in RLQ with an intentionally delayed appendectomy after antibiotics Medical record review if hospitalized Phone follow-up 1-2 weeks
OUTCOME	Proportion with appendicitis for each PAS level stratified by ultrasound result Proportion with appendicitis for PAS defined as low, moderate or high stratified by ultrasound result
DESIGN	Observational: Prospective cohort

ARE THE RESULTS VALID?

Did participating patients present a diagnostic dilemma?	Yes. Patients were seen in the ED with clinical “suspicion” of appendicitis requiring imaging or surgical consultation.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The reference standards were: 1. Intraoperative findings and pathologic findings for those undergoing appendectomy 2. Cross sectional imaging indicating abscess in the RLQ in those with a delayed appendectomy after antibiotics 3. Medical record review if hospitalized 4. Phone follow-up within 1-2 week
Were those interpreting the test and reference standard blind to the other results?	Yes, those reading the ultrasound were temporally blinded to the final diagnosis. Attendings completed the clinical and physical questionnaire before the advanced imaging. It is unclear but probable that the ultrasound results were utilized by the surgeons and ED physicians to determine the need for operative intervention. However, it is unlikely that this would bias the interpretation of the objective criterion standard as only surgical operative notes were used for ruptured appendix, the rest was pathology reports.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	No. It would have been unethical to bring every patient to the operating room. Follow up was used as a surrogate measure. Patients were followed up either medical record review if admitted or telephone follow up if discharged. Nine percent were not available for follow up.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 728, 29% with appendicitis, 13% perforated
22% of ultrasounds performed were equivocal
23% of the patients with an equivocal ultrasound had appendicitis

TABLE 3: PROPORTION WITH APPENDICITIS

	ULTRASOUND FINDINGS		
PAS SCORE	POSITIVE	NEGATIVE	EQUIVOCAL
Low: 0-3	73% (47, 99%)	0% (0, 3%)	9% (0, 19%)
Medium: 4-6	90% (82, 98%)	6% (3, 9%)	13% (5, 21%)
High: 7-10	97% (95, 100%)	19% (11, 27%)	47% (33, 61%)

A low PAS score and a negative ultrasound effectively rules out appendicitis (0%) though the upper limit of the confidence interval is 3%

A high PAS score and a positive ultrasound effectively rules in appendicitis (97%) The lower limit of the confidence interval is 95% so this could result in a negative laparotomy rate as high as 5%.
When there is discordance between the PAS score and ultrasound, for example with a high PAS score and negative ultrasound, the results are less likely to assist in determining management. These patients may require additional imaging or admission for serial examinations.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	The radiologists were attending pediatric radiologists. It would have been nice to have a kappa statistic to measure of interrater reliability because the performance of ultrasound depends on experience. There was no kappa or interrater agreement on either the radiographic or clinical findings and some of the PAS score criteria are somewhat subjective.
Are the study results applicable to the patient in my practice?	Yes. The patient description included demographic characteristics were reported. However, there was no set criteria for referral for ultrasound.
Will the results change my management strategy?	It helps to further stratify patient risk. Discordant or equivocal results between the test and clinical assessment will lead to further investigation or observation. However, this doesn't change my current management strategy.
Will patients be better off as a result of the test?	The study's conclusions suggest that ultrasound findings be correlated with clinical assessment. It has the potential to decrease radiation from CT scans at the risk of rarely missing patients with appendicitis.

CLINICAL BOTTOM LINE

BACKGROUND: Pediatric patients who present to the ED with a clinical picture suggestive of appendicitis represent a difficult diagnostic decision for ED physicians. Currently the imaging of choice to diagnose appendicitis is ultrasound. However, a large proportion of the time the ultrasound does not definitively identify the appendix and the results is considered equivocal. The objective was to determine the diagnostic accuracy of ultrasonography (US) for appendicitis in children when combined with clinical and laboratory assessment based on the Pediatric Appendicitis Score (PAS).

CLINICAL QUESTION: In children with suspected appendicitis can a combination of radiologist performed ultrasonography (US) and the Pediatric Appendicitis Score (PAS) be used to adequately distinguish between those with and without appendicitis?

DESIGN/VALIDITY: This study is an observational cohort study of children presenting with possible appendicitis. A convenience sample of 728 patients were enrolled (29% with appendicitis and 13% with a perforate appendicitis) based on chief complaint. During the classification of the ultrasound results, reports indicating that the appendix was not visualized but there were no secondary signs of appendicitis also were considered negative. One might classify this as equivocal and not as a negative ultrasound. I would have like to include the physician assessment of likelihood of appendicitis before any imaging. As PAS score can change through the course of a patient's ED stay, a change in the PAS score would have been helpful (e.g. PAS score at the time ultrasound results were available).

PRIMARY RESULTS: Ultrasound was positive in 160/728 (22%), equivocal in 160/728 (22%) and negative in 408/728 (56%) of the study patients. 29% of the patients had appendicitis. Importantly, 23% of the patients with an equivocal ultrasound had appendicitis. The equivocal results prevent the calculation of sensitivity, specificity and likelihood ratios. The study only provides test characteristics when an equivocal ultrasound result is combined with either a positive or negative ultrasound. Otherwise the study presents predictive values.

When there is concordance between the PAS score and ultrasound then clinical decision-making is facilitated. A low PAS score and a negative ultrasound effectively ruled out appendicitis (0%) though the upper limit of the confidence interval is 3%. In this situation, the patient can likely be discharged with appropriate follow up and return precautions. A high PAS score and a positive ultrasound effectively ruled in appendicitis (97%) though the lower limit of the confidence interval is 95%. These patients likely require an appendectomy without further imaging or observation.

APPENDICITIS RISK: PEDIATRIC APPENDICITIS SCORE AND ULTRASOUND

	ULTRASOUND FINDINGS		
	POSITIVE	NEGATIVE	EQUIVOCAL
PAS Low: 0-3	73% (47-99)	0% (0-3)	9% (0-19)
PAS Medium: 4-6	90% (82-98)	6% (3-9)	13% (5-21)
PAS High: 7-10	97% (95-100)	19% (11-27)	47% (33-61)

When there is discordance between the PAS score and ultrasound, for example with a high PAS score and negative ultrasound, the results are less likely to assist in determining management. These patients may require additional imaging or admission for serial examinations.

APPLICABILITY: This was a single center study. The patient description included a wide range of demographic characteristics. However, there was no set criteria for referral for ultrasound. There was no kappa or interrater agreement on either the radiographic or clinical findings and some of the PAS score criteria are somewhat subjective.

AUTHOR'S CONCLUSIONS: "Ultrasound findings in children with possible appendicitis should be integrated with clinical assessment, such as a clinical score, to determine next steps in management. Rates of false-negative US increase with increasing PAS, and false-positive US results occur more often with lower PAS. When discordance exists between US results and the clinical assessment, serial examinations or further imaging are warranted."

POTENTIAL IMPACT: The correlation of clinical and laboratory findings (PAS score) and ultrasound results can assist is determining the post-test probability of appendicitis. For example, when there is a low PAS score and a negative ultrasound then the risk of appendicitis was 0% (0-3%). The combination of the two should not be relied upon when the results of each are discordant (a high PAS score and ultrasound negative for appendicitis) or when the ultrasound result is equivocal. Coordination with our surgical colleague and early follow-up for those discharged is essential.

APPENDIX: PEDIATRIC APPENDICITIS SCORE

PEDIATRIC APPENDICITIS SCORE	POINTS
Anorexia	1
Nausea or vomiting	1
Migration of pain	1
Fever (> 38 C)	1
Tenderness over the right iliac fossa	2
Cough/percussion/hopping tenderness in the RLQ	2
Leukocytosis (> 10,000/ml^3)	1
Polymorphonuclear neutrophilia (> 7,500/ml^3)	1

APPENDICITIS:
POINT-OF-CARE ULTRASOUND

In a pediatric patient with suspected appendicitis, does a point of care ultrasound performed by pediatric emergency medicine physicians decrease emergency department length of stay and utilization of CT scans?

Dana Suozzo, M.D., Michael Mojica, M.D.
March 2014

Elikashvili I, Tay ET, Tsung JW.

THE EFFECT OF POINT-OF-CARE ULTRASONOGRAPHY ON EMERGENCY DEPARTMENT LENGTH OF STAY AND COMPUTED TOMOGRAPHY UTILIZATION IN CHILDREN WITH SUSPECTED APPENDICITIS.

Acad Emerg Med. 2014 Feb;21(2):163-70.
PubMed ID: 24673672

STUDY DEFINITIONS	
POPULATION	Inclusion < 21 years old, suspected appendicitis requiring laboratory or ultrasound evaluation Exclusion Prior diagnosis of appendicitis, prior diagnosis of inflammatory bowel disease, prior CT or ultrasound for current abdominal pain, unstable vital signs, life threatening illness requiring resuscitation Setting: Single Pediatric ED. 5/2011-10/2012
INTERVENTION	Point of Care ultrasound performed by pediatric emergency physicians 1 hour of training – ½ hour didactic and ½ hour hands on Varying prior experience with ultrasound for appendicitis (< 25 scans = novice) Ultrasound (+): Non-compressible tubular structure visualized from tip of cecum and > 6 mm in diameter Ultrasound (-): Compressible tubular structure visualized in perpendicular orthogonal plains from tip of cecum < 6 mm in diameter Ultrasound (equivocal): US neither positive or negative by above criteria
CONTROL	Operative findings, biopsy or Clinical follow up at 3 weeks
OUTCOME	Time to disposition, CT rate, Test characteristics
DESIGN	Observational: Prospective cohort

ARE THE RESULTS VALID?	
Did participating patients present a diagnostic dilemma?	Yes. The patients in the study were suspected of having appendicitis. This was defined as requiring an imaging evaluation.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The outcomes were determined by operative or pathology reports in those with appendicitis, and at approximately 3-week phone follow-up for non-operative patients
Were those interpreting the test and reference standard blind to the other results?	Yes. The point of care ultrasound was done prior to other confirmatory tests or phone follow-up therefore ED ultrasound was blinded to the outcome. It is unclear if operative reports could be biased by knowledge of prior imaging. Phone follow up was conducted with knowledge of scan results.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	No. This study had multiple reference standards. Not all patients with a positive or an equivocal point-of-care ultrasound were taken to the operating room. It would have been unethical to subject all patients to surgery. A 3-week phone follow-up was used as an alternative.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

		APPENDICITIS		
		YES	NO	
POINT OF CARE ULTRASOUND	POSITIVE	30	5	35
	NEGATIVE*	20	95	115
		50	100	150

*Equivocal scans were considered negative for analysis
104/150 (70%) were equivocal scans

TEST CHARACTERISTICS (95% CONFIDENCE INTERVAL)	
Prevalence	33% (50/150)
Sensitivity	60% (30/50), 95% CI (46.2, 72.4%)
Specificity	95% (95/100), 95% CI (88, 97.3%)
Predictive Value (+) Test	88% (30/35), 95% CI (71, 94%)
Predictive Value (-) Test	83% (95/115), 95% CI (75, 89%)
Likelihood Ratio (+) Test	12 (30/50)/(5/100), 95% CI (4.6, 23.34)
Likelihood Ratio (-) Test	0.42 (20/50)/(95/100) , 95% CI (0.30, 0.59)

ED Length of Stay (Table 2)
Point of Care US Disposition (n=25): 154 min (113, 195)
Radiology US: 288 min (256, 319)
CT- 487 min (434, 540)

CT Rate
Prior to radiology ultrasound implementation: 75.8%
After radiology ultrasound implementation: 44.2%
Study rate with point of care ultrasound: 27.3%

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	Perhaps. This depends on the novice's ability to identify the appendix. Experienced operators were found to have a greater sensitivity (80% vs 51%) and specificity (97.8% vs 92.6%) when compared to novice sonologists. (Table 4). The majority of false positives and false negatives occurred at the beginning of the study. These finding make additional training and/or experience necessary.
Are the study results applicable to the patient in my practice?	Yes. The patients in the study have similar demographic and clinical characteristics (age, h/o fever & n/v, maximal tenderness in RLQ) to patients seen at our institution. There could be differences in prevalence rates at our institution compared to the ~30% prevalence rate reported at the study institution. Reporting of the percentage of patients with perforation or abscess would have allowed for an assessment of the potential for spectrum bias.
Will the results change my management strategy?	The results of this study will encourage physicians to perform more RLQ POC US. No patients who were discharged after a negative or equivocal POC US (n=25 or 16%) were found to have appendicitis at 3-week phone follow up. Whether pediatric surgeons will require further imaging after a positive POC US needs to be determined. Patients may still be referred for radiology US or CT scan for confirmation prior to taking a patient to the operating room.
Will patients be better off as a result of the test?	Patients may benefit by use of POC US. A positive result can decrease the amount of time spent in the emergency room, decrease exposure to radiation, and decrease time for definitive management/operating room.

CLINICAL BOTTOM LINE

BACKGROUND: Ultrasound has been found to decrease CT rates in pediatric patients with suspected appendicitis. Point of care ultrasound by pediatric emergency physicians has the potential to decrease ED length of stay.

CLINICAL QUESTION: In a pediatric patient with suspected appendicitis, does a point of care ultrasound performed by pediatric emergency medicine physicians decrease emergency department length of stay and utilization of CT scans?

DESIGN/VALIDITY: This was a well-designed study without significant validity concerns. It included 150 patients 33% of which had appendicitis. The most difficult question is what to do with the 70% of patients with an equivocal scan. 18% (19/104) of patients with equivocal scans were found to have appendicitis. In this study, the equivocal scans were considered negative for the purpose of analysis. 82% (85/104) of patients with equivocal scans underwent additional imaging. This is the same proportion of patients undergoing additional imaging with a negative POC US. (82%, 8/11) though the appendicitis prevalence was only 9% (1/11) in this population.

PRIMARY RESULTS: The study found a statistically significant reduction in ED length of stay for those patients whose disposition was determined by point of care ultrasound (154 min) when compared to patients requiring radiology ultrasound (288 min) and or CT (487 min). There was a non-significant decrease in the CT rate (44.2% vs 27.3%) during the study.

The POC US demonstrated poor overall sensitivity (60%) and reasonable overall specificity (94%). Experience sonologists had better test characteristics (Sensitivity 80%, Specificity 97.8%) though the rate of equivocal scans was equivalent (67%)

APPLICABILITY: The primary applicability concern is the difficulty in locating the appendix. 70% of the POC US scans were equivocal as were 60% of the radiology ultrasounds. Experience improved test performance.

AUTHOR'S CONCLUSION: "It may be feasible to reduce ED length of stay and avoid a computed tomography scan when using point-of-care ultrasound to evaluate children with suspected appendicitis. Test characteristics for point-of-care ultrasound have high specificity to rule in appendicitis, similar to radiology ultrasound. Addition of point-of-care ultra- sound prior to sequential radiology imaging was safe, without missed cases of appendicitis or negative laparotomies."

POTENTIAL IMPACT: Point of care ultrasound should be used to develop experience in the pediatric ED. Users with significant training and experience can have test characteristics similar to those of a radiology ultrasound. Consultation with radiologists and pediatric surgeons needs to occur before point of care ultrasound can be integrated into a management strategy in pediatric patients with suspected appendicitis.

APPENDICITIS:
RADIOLOGY ULTRASOUND

In pediatric patients aged 3 to 18 years who present with acute abdominal pain concerning for appendicitis:
1. What is the test performance of radiology department performed ultrasound?
2. Does test performance vary in relation to frequency of ultrasound use at individual institutions?
3. Does test performance change when the appendix (normal or abnormal) is definitively identified?

Rebecca Burton, M.D., Adriana Manikian, M.D.

August 6, 2013

Mittal MK, Dayan PS, Macias CG, Bachur RG, Bennett J, Dudley NC, Bajaj L, Sinclair K, Stevenson MD, Kharbanda AB; Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics.

PERFORMANCE OF ULTRASOUND IN THE DIAGNOSIS OF APPENDICITIS IN CHILDREN IN A MULTICENTER COHORT.

Acad Emerg Med. 2013 Jul;20(7):697-702.
PubMed ID: 23859583

STUDY DEFINITIONS	
POPULATION	Inclusion: 3 to 18 years, acute abdominal pain (< 96 hours), suspected appendicitis (laboratory studies, imaging (CT or ultrasound), and/or surgical consultation) Exclusion: Pregnancy, prior abdominal surgery, chronic gastrointestinal illness or abdominal pain, sickle cell anemia, cystic fibrosis, medical condition limiting the ability to obtain an accurate history, history of abdominal trauma within 7 days, imaging of the abdomen performed prior to ED arrival Setting: Multicenter (n=8): Pediatric Emergency Medicine Collaborative Research Committee, 3/2009-4/2010
TEST	Attending pediatric radiologist performed abdominal ultrasound Positive US: Appendicitis or perforated appendicitis, based on visualization of an abnormal appendix with or without secondary signs Negative US: Normal, appendix not visualized, equivocal and other
REFERENCE STANDARD	Appendectomy group: Pathology, attending surgeon's intraoperative findings Non-Operative group: 2-week phone follow-up, If unreachable then medical record reviewed for revisits within 3 months
OUTCOME	Test characteristics (overall, when appendix visualized, per institution)
DESIGN	Observational: Secondary analysis of a prospective cohort

ARE THE RESULTS VALID?	
Did participating patients present a diagnostic dilemma?	Yes. Participating patients were children aged 3 to 18 years who presented with acute abdominal pain of < 96 hours' duration and who had laboratory studies, imaging (CT or ultrasound), and/or surgical consultation obtained for "suspected appendicitis."
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The reference standard in this study was one of three things: 1. Operative pathology 2. Attending Surgeon's Intraoperative findings 3. For non-operative patient's, phone follow up at 2 weeks. If unreachable by phone, then medical record reviewed for revisits within 3 months Though there are three, rather than one, reference standards in this study, they are appropriate and independent from the diagnostic test under investigation. Pathology and operative findings are objective in nature, unlikely to be influenced by whether the ultrasound was positive, negative, or equivocal. Phone follow-up and medical record review was an appropriate alternative for those children who did not go to the OR, as it would be unethical to have an operative intervention in all patients.
Were those interpreting the test and reference standard blind to the other results?	No. The authors explicitly state that the radiologists performing and interpreting the ultrasound studies "were not blinded to clinical team input or final outcomes." It is unlikely that the surgeons performing laparotomy and subsequently writing operative reports were blind to imaging results. It is unclear whether the pathologists evaluating surgical specimens or the individuals performing phone follow up and medical record review were blind to ultrasound results, though it is never explicitly stated that they were blinded.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	As stated above, there are three reference standards in this study. The reference standards appear to be appropriate and independent from the diagnostic test under investigation. Pathology and operative findings are objective in nature, unlikely to be influenced by whether the ultrasound was positive, negative, or equivocal. Phone follow-up and medical record review was an appropriate alternative for those children who did not go for laparotomy, as it would be unethical to send all children to the OR. However, the study authors fail to report how many of the patient population fell into each category of reference standard, or how many patients were lost to follow up.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

	APPENDICITIS		
	POSITIVE	NEGATIVE	
ULTRASOUND POSITIVE	235	19	254
ULTRASOUND NEGATIVE*	89	622	711
	324	641	
*Appendix not visualized = Negative US			

Test Characteristics: Appendix not visualized = Negative Ultrasound:
Sensitivity: 235/324 = 72.5%, 95% CI (58.8%, 86.3%)
Specificity: 622/641 = 97.0%, 95% CI (96.2%, 97.9%)
Predictive Value Positive Test: 235/254 = 92.5%, 95% CI (87.4%, 97.7%)
Predictive Value Negative Test: 622/711 = 87.5%, 95% CI (84.3%, 90.7%)
Likelihood Ratio Positive Test: (235/324)/(19/641) = 24.5, 95% CI (15.6, 38.3)
Likelihood Ratio Negative Test: (89/324)/(622/641) = 0.28, 95% CI (0.24, 0.34)

Test Characteristics: Appendix Definitively Identified:
Sensitivity: 97.9%, 95% CI (95.2%, 99.9%)
Specificity: 91.7%, 95% CI (86.7%, 96.7%)
Predictive Value Positive Test: 92.5%, 95% CI (87.4%, 97.7%)
Predictive Value Negative Test97.7%, 95% CI (94.7%, 99.9%)
Likelihood Ratio Positive Test: 11.8, 95% CI (7.7, 18.2)
Likelihood Ratio Negative Test: 0.02, 95% CI (0.009, 0.05)

VARIATION ACROSS SITES BY FREQUENCY OF US USE			
SITE	ULTRASOUND USAGE	SENSITIVITY	ID APPENDIX
A, B, C	89-94%	77.7%	56%
D	51%	51.6% (33-70.2%)	25%
E, F, G, H	9%	35% (20-50%)	26%

This was not a meta-analysis though the results of each study were combined despite the heterogeneity of study results

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	Unclear. As the authors demonstrate, and as is widely observed, ultrasound for appendicitis is extremely operator dependent. At four of the eight study sites, ultrasound was available 24 hours a day, 7 days a week, and was used as the first-line imaging study for evaluation of appendicitis in 89-94% of cases. At these sites, sensitivity ranged anywhere from 69 to 86%, with a combined sensitivity of 77.7%, somewhat improved from the overall sensitivity of 72.5% determined across all 8 sites. At these four high use sites, the appendix was definitively identified in 56% of cases. This is important, as when study authors performed a subgroup analysis of cases where the appendix (whether normal or abnormal) was definitively identified, test characteristics changed, with significant improvement in sensitivity (to 97.9% from 72.5%), NPV (to 97.7% from 87.5%), and LR- (to 0.02 from 0.28). At the same time, specificity decreased slightly (to 91.7% from 97.0%), PPV was unchanged at 92.5%, and LR+ decreased (from 24.5 to 11.8). In contrast, at the one site where ultrasound was available in the daytime only, and was used in 51% of cases, sensitivity was only 51.6% and the appendix was definitively identified in only 25% of cases. At the four sites with infrequent ultrasound use, in about 9% of total cases, ultrasound test performance characteristics were even worse: sensitivity was 35%, and the appendix was definitively identified in 26% of cases. Patient centered factors such as age and body mass index also influence the ability to obtain adequate images via ultrasound, and it is possible that our ED population, which includes older (18-24 years old) patients and patients with more adipose tissue, will present further challenges to the widespread use of ultrasound for diagnosis of appendicitis. Finally, inter-rater reliability as reflected by kappa values were not reported by the study authors. This makes it unclear how well study results apply to other populations, including ours. At our institution, ultrasound for appendicitis is becoming more widely used, and is part of the official protocol for the imaging evaluation of suspected appendicitis, but there is likely still significant room for improvement. As our radiologists and potentially PEM physicians become more adept at using ultrasound in the evaluation of suspected appendicitis, there is potential for this imaging modality to have a critical role in the evaluation of children with acute abdominal pain concerning for appendicitis.
Are the study results applicable to the patient in my practice?	Yes. In our Pediatric Emergency Service we see many patients who present with acute abdominal pain concerning for possible appendicitis.

Will the results change my management strategy?	The study results will perhaps reinforce the use of ultrasound in the evaluation of suspected appendicitis, as our department is already on board with utilizing this imaging modality.
Will patients be better off as a result of the test?	Potentially yes. Children and adolescents who present with acute appendicitis often undergo abdominal/pelvic CT as part of their evaluation. CT scanning is not only associated with long term malignancy risk due to exposure to ionizing radiation, but also is often associated with risks related to receiving intravenous contrast as well. Accurately diagnosing or excluding acute appendicitis via ultrasound, an imaging modality associated with minimal (if any) risks to the patient), rather than CT, has significant potential to benefit the patient.

CLINICAL BOTTOM LINE

BACKGROUND: Acute abdominal pain is common in the pediatric population and it presents a significant diagnostic dilemma. In addition to clinical and laboratory assessment, imaging studies are often an essential component of the evaluation of the child or adolescent with acute abdominal pain. In recent years, ultrasound has become an appealing potential alternative imaging modality to CT scanning for the diagnosis or exclusion of appendicitis, as it obviates exposure to ionizing radiation and intravenous contrast.

CLINICAL QUESTION: In pediatric patients aged 3 to 18 years who present with acute abdominal pain concerning for appendicitis:
1. What is the test performance of radiology department performed ultrasound?
2. Does test performance change in relation to frequency of ultrasound use at individual institutions?
3. Does test performance change when the appendix is definitively identified?

DESIGN/VALIDITY: This study is a secondary analysis of a prospective, multicenter observational cohort study performed at 8 Pediatric Emergency Departments within pediatric tertiary care centers with a sample size of 965 patients. This study was well designed without major methodologic flaws.

PRIMARY RESULTS: This study demonstrated very good test performance characteristics for ultrasound in the diagnosis of appendicitis, particularly when the appendix was definitively identified. Over the entire study sample, ultrasound sensitivity was 72.5%, specificity 97.0%, PPV 92.5%, NPV 87.5%, LR+ 24.5, and LR- 0.28. Given a pre-test probability of appendicitis of approximately 33% in the study population, a positive test with a LR+ of 24.5 puts the patient's post-test probability of appendicitis at about 94%, and a negative test with a LR- of 0.28 puts the patient's post-test probability of appendicitis at about 11%. When the appendix is definitively identified, a negative test with a LR- of 0.002 puts the patient's post-test probability of appendicitis at 0%.

	APPENDIX NORMAL NOT VISUALIZED	APPENDIX DEFINITIVELY IDENTIFIED
Sensitivity	72.5% (58.8, 86.3%)	97.9% (95.2, 99.9%)
Specificity	97.0% (96.2, 97.9%)	91.7% (86.7, 96.7%)
Predictive Value (+) Test	92.5% (87.4, 97.7%)	92.5% (87.4, 97.7%)
Predictive Value (-) Test	87.5% (84.3, 90.7%)	97.7% (94.7, 99.9%)
Likelihood Ratio (+) Test	24.5 (15.6, 38.3)	11.8 (7.7, 18.2)
Likelihood Ratio (-) Test	0.28 (0.24, 0.34)	0.02 (0.009, 0.05)

APPLICABILITY: Ultrasound for appendicitis is user dependent. The authors identified that sites with a high percentage usage of ultrasound could definitively identify the appendix more frequently and have a higher sensitivity. Inter-rater agreement for ultrasound interpretation was not presented.

AUTHOR'S CONCLUSION: "Ultrasound had an overall lower sensitivity in diagnosing appendicitis in children in this multicenter cohort than in previous reports. There was a large variation in rates of identification of the appendix and sensitivity for diagnosing appendicitis across sites, with lower rates at centers that used ultrasound less frequently. Ultrasound had high sensitivity and specificity, however, across all sites when the appendix was clearly identified. Other diagnostic modalities should be considered when US does not identify the appendix clearly."

POTENTIAL IMPACT: This study demonstrates that ultrasound has significant potential as an imaging study in the evaluation of patients with suspected appendicitis. However, ultrasound test performance varied considerably depending on frequency of use at different study sites, with sites utilizing ultrasound as the first-line imaging study demonstrating much better overall diagnostic test performance characteristics. In cases where the appendix (whether normal or abnormal) was definitively identified, ultrasound had high sensitivity and specificity, and strong likelihood ratios. In cases where the appendix is unable to be visualized, other evaluation strategies such as serial abdominal exams and/or other imaging studies (such as CT) could be employed. The avoidance of radiation from CT needs to be balanced against the better ability of CT to identify alternative diagnosis and ultrasounds inability to definitively identify the appendix a major proportion of the time.

APPENDICITIS:
RISK CALCULATOR DERIVATION

In pediatric patients 5 to 18 years of age with acute abdominal pain and suspected appendicitis, how accurately does the Pediatric Appendicitis Risk Calculator (pARC) quantify the risk of appendicitis? Additionally, how does the pARC equation perform when compared with the Pediatric Appendicitis Score (PAS)?

Ellen Duncan, MD, PhD, Michael Mojica, MD

October 2018

Kharbanda AB, Vazquez-Benitez G, Ballard DW, Vinson DR, Chettipally UK, Kene MV, Dehmer SP, Bachur RG, Dayan PS, Kuppermann N, O'Connor PJ, Kharbanda EO.

DEVELOPMENT AND VALIDATION OF A NOVEL PEDIATRIC APPENDICITIS RISK CALCULATOR (pARC)

Pediatrics Apr 2018, 141 (4) e20172699
PubMed ID: 29535251

STUDY DEFINITIONS	
POPULATION	Inclusion: 5-18 years, presenting with acute (< 96 hours) abdominal pain, evaluated for suspected appendicitis by labs, imaging, or surgical consultation. Exclusion: Pregnancy, previous abdominal surgery, inflammatory bowel disease, chronic pancreatitis, sickle cell anemia, cystic fibrosis, history of abdominal trauma within previous 7 days or medical condition affecting ability to obtain an accurate history. Setting: Derivation: 9 pediatric emergency departments, 3/2009-4/2010 Validation: Single (different) pediatric ED, 2003-2004 and 2013-2015
RULE PARAMETERS	Demographic: Age, sex History: Duration of pain, history of nausea or emesis, migration of pain to RLQ, pain with walking, coughing, or hopping Examination: Fever (> 38 C) in the ED, maximum tenderness in RLQ, abdominal guarding Laboratory: WBC and ANC
REFERENCE STANDARD	Diagnosis of appendicitis 1. Operative patients: Pathology report 2. Non-operative patients: Phone follow up or medical record review
OUTCOME	Area under the receiver operating characteristic curve for pARC and PAS
DESIGN	Observational: Prospective cohort (derivation), retrospective cohort (validation)

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. Predictive variables were: gender, age, duration of pain, history of nausea or emesis, migration of pain to RLQ, maximum tenderness in RLQ, abdominal guarding, or pain with walking, coughing, or hopping. Laboratory indicators included WBC and ANC. No. Fever was not included in the analysis due to 18% missing data. Anorexia was not included in the derivation process. This is important because these were significant predictors in both the Alvarado and Pediatric Appendicitis scores.
Were all important predictors present in significant proportion of the study population?	Yes. (Table 1) Most of the predictors were present in a significant proportion of the study population. The lowest proportion was females 5-7.9 years of age (validation: 8%, derivation: 9%).
Were the outcome event and predictors clearly defined?	Yes. The primary outcome was clearly defined as appendicitis on pathology for patients who underwent appendectomy, or appendicitis either on phone follow up or medical chart review for non-operative patients. However, the proportion of non-operative patients available for phone follow-up was not presented. Review of medical records could potentially miss patients returning for care outside of the initial hospital system
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Outcomes Predictors: Clinicians collecting the predictors were temporally blinded to the outcome. Predictors: It is likely, that the pathologists were blinded to the predictors though this is not explicitly stated. If the pathologists were not blinded to the predictors it is unlikely that this would affect the interpretation of the appendicitis outcome. It is also unclear whether outcome assessors of those not undergoing appendectomy were blinded to the predictors.
Was the sample size adequate (including an adequate number of outcome events)?	Yes. The populations were both large, with 2,423 patients in the derivation cohort (40% appendicitis) and 1,426 patients in the validation cohort (35% appendicitis). Additionally, table 3 shows 10 different predictors, and the derivation cohort included close to 1,000 patients with appendicitis. This exceeds the general rule for logistic regression that there be 10 outcomes per predictor.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SENSITIVITY AND PREDICTIVE VALUE OF A NEGATIVE RULE WITH 95% CONFIDENCE INTERVALS)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SPECIFICITY AND PREDICTIVE VALUE OF A POSITIVE RULE WITH 95% CONFIDENCE INTERVALS)

Derivation cohort: 2,432 (40% appendicitis)
Validation cohort:1,426 (35% appendicitis)

Included in final equation: Age, sex, duration of pain, migration of pain to RLQ or pain with walking, coughing, or hopping, maximum tenderness in RLQ, abdominal guarding, WBC, and ANC
Not included in final equation: History of nausea or emesis, fever (>38C) in the ED.

The test characteristics of the validation cohort are presented in the table below. The authors did not present the test characteristics of the derivation cohort for comparison.

TABLE 4: TEST CHARACTERISTICS (VALIDATION COHORT)

	Risk*	% AP	% PT	SN	SP	PV (+)	PV (-)	Missed	(-) Lap
Low Risk	< 5%	5%	20%	100%	0.0%	34.6%	99.6%	0.4%	8.8%
	5-14%	10%	22%	97.2%	28.7%	41.9%	99.6%	0.4%	7.7%
Intermediate Risk	15-24%	23%	12%	90.7%	58.7%	53.7%	99.4%	0.6%	6.8%
	25-49%	42%	18%	82.8%	72.5%	61.4%	99.2%	0.8%	5.2%
	50-74%	62%	16%	60.2%	88.8%	73.7%	98.8%	1.2%	5.5%
	75-84%	78%	6%	32.3%	97.5%	87.4%	98.9%	1.1%	2.6%
High Risk	≥ 85%	97%	6%	17.8%	99.7%	96.7%	100%	0%	1.2%

*Consensus based “clinically actionable” risk categories

Area Under the ROC (AUC): pARC = 0.85, 95% CI (0.83, 0.87)
Area Under the ROC (AUC): PAS = 0.77, 95% CI (0.75, 0.80)
A statistical comparison of the two areas under the curve was not presented.

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

The pARC score classified 48% of the patients as either high risk (risk ≥ 85%, 6% of patients) or low risk (risk < 15%, 42% of patients). If low-risk patients were discharged or observed without imaging and high-risk patients taken to the OR without imaging then there is a potential to reduce imaging. Imaging could be limited to intermediate-risk patients (risk 15-84%, 54% of patients). This is lower than the proportion classified as intermediate risk (3-6) by the pediatric appendicitis score (up to 70% in some studies). The rate of ultrasound utilization in the study was 37%. The study rate of CT utilization was not presented so that the total rate of imaging (US + CT) could not be determined for comparison.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

No. There was no internal validation.
There was a retrospective, external validation cohort. The validation cohort consisted of patients 5-18 years of age who presented to a single center between 2003-2004 and 2013-2015. This cohort was chosen due to similar criteria to the derivation cohort for cohort entry, data collection, data cleaning and quality control. Importantly, the validation population was at a different center than the derivation population. Table 1 indicates that the derivation and validation cohort were similar with regard to age and sex. However, nausea/vomiting, migration of pain and pain with walking/hopping were greater in the derivation cohort. 40% of the derivation cohort and 35% of the validation cohort had appendicitis. The authors did not include the rates of perforated appendicitis within each cohort. This is important since the extent of illness may impact the test characteristics (spectrum bias).

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (See Appendix)	☐ I ☐ II ☐ III ■ IV Derivation Cohort: Multicenter (n=9), prospective Validation Cohort: Single center, retrospective The rule requires further prospective validation, preferably multicenter, before it can be applied clinically.
Does the rule make clinical sense?	Yes. The predictors included in the equation are those that are often used to assess for the likelihood of appendicitis. The presence of fever was excluded due to missing data. Nausea/vomiting was not a significant predictor in the model. Anorexia was not included in the derivation process.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. The authors included “moderate” interrater reliability (kappa >0.35) which would be considered “fair” by others. The kappa for the individual physical exam predictors (RLQ tenderness, rebound), that would be the most open to interpretation, were not presented. Additionally, there is no tool with which to determine the score, which significantly limits its use. The authors admit that the calculator is not intuitive and requires sophisticated calculations and suggest programming the pARC into the electronic medical record.
Is the rule applicable to the patients in my practice?	Yes. The characteristics of the derivation and validation cohorts (table 1) are similar to our patient populations in terms of demographics and presenting signs and symptoms. However, the rates of appendicitis of these two cohorts were 40% and 35% respectively, which may differ from our rates. The equation may not be applicable to patients with suspected appendicitis in non-Children’s hospital settings.
Will the rule results change my management strategy?	Unclear. A low risk of <15% may represent too high a risk not to obtain imaging. Additionally, 3% of patients classified in the highest risk category did not have appendicitis, which represents a negative laparotomy rate may not be acceptable to our surgical colleagues. The rule is not likely to immediately change our management strategy unless it is validated.
What are the benefits of applying the rule to my patients?	The pARC more accurately identifies patients with both the lowest and highest risk of appendicitis, which could aid in guiding management decisions regarding imaging and consultation.
What are the risks of applying the rule to my patients?	As above, patients with appendicitis who score in the low-risk group may be missed, and patients in the high-risk group in whom imaging is deemed unnecessary may be taken to the operating room needlessly.

CLINICAL BOTTOM LINE

BACKGROUND: Appendicitis is a common pediatric surgical emergency, and many clinical scoring mechanisms have been derived to guide evaluation of patients for possible appendicitis. The risk stratification is especially important, as imaging for the diagnosis of appendicitis includes ultrasound (no radiation, high rate of equivocal results, often with a delay in obtaining imaging and results that operator-dependent) and CT (ionizing radiation, may be performed more often than necessary).

CLINICAL QUESTION: In pediatric patients 5 to 18 years of age with acute abdominal pain and suspected appendicitis, how accurately does the Pediatric Appendicitis Risk Calculator (pARC) quantify the risk of appendicitis? Additionally, how does the pARC equation perform when compared with the Pediatric Appendicitis Score (PAS)?

DESIGN/RISK OF BIAS: This was a well-designed, multicenter, prospective derivation and single center retrospective validation of an appendicitis risk calculator. Prediction variables were: gender, age, duration of pain, history of nausea or emesis, migration of pain to RLQ, maximum tenderness in RLQ, abdominal guarding, or pain with walking, coughing, or hopping. Laboratory indicators included WBC and ANC. Fever was not included in the analysis due to 18% missing data. Anorexia was not included in the derivation process. This is important because these are significant predictor in both the Alvarado and Pediatric Appendicitis scores. The primary outcome was clearly defined as appendicitis on pathology for patients who underwent appendectomy, or appendicitis either on phone follow up or medical chart review for non-operative patients. However, the proportion of non-operative patients available for phone follow-up was not presented. Review of medical records could potential miss patients returning for care outside of the initial hospital system.

Nausea/vomiting, migration of pain and pain with walking/hopping were more common in the derivation cohort. The authors did not present the rates of perforated appendicitis within each cohort. This is important since the extent of illness may impact the test characteristics (spectrum bias).

PRIMARY RESULTS: The derivation cohort included 2,432 patients (40% appendicitis) and the validation cohort included 1,426 patients (35% appendicitis). Predictors included in the final equation were: age, sex, duration of pain, migration of pain to RLQ or pain with walking, coughing, or hopping, maximum tenderness in RLQ, abdominal guarding, WBC, and ANC. The pediatric appendicitis risk calculator had an area under the ROC curve of 0.85, 95% CI (0.83, 0.87) compared to the area under the ROC curve for the pediatric appendicitis score of 0.77, 95% CI (0.75, 0.80). The test characteristics and area under the curve are presented only for the validation cohort. Typically, they are compared to the test characteristics in the derivation cohort.

The pARC score classified 48% of the patients as either high risk (risk ≥ 85%, 6% of patients) or low risk (risk < 15%, risk, 42% of patients). If low-risk patients were discharge or observed without imaging and high-risk patients taken to the OR without imaging then there is a potential to reduce imaging. Imaging could be limited to intermediate-risk patients (risk 15-84% 54% of patients). This is lower than the proportion classified as intermediate risk (3-6) by the pediatric appendicitis score (up to 70% in some studies). The rate of ultrasound utilization in the study was 37%. The rate of CT utilization in was not presented for comparison.

TABLE 4: TEST CHARACTERISTICS (VALIDATION COHORT)									
	Risk*	% AP	% PT	SN	SP	PV(+)	PV (-)	Missed	(-) Lap
Low Risk	< 5%	5%	20%	100%	0.0%	34.6%	99.6%	0.4%	8.8%
	5-14%	10%	22%	97.2%	28.7%	41.9%	99.6%	0.4%	7.7%
Intermediate Risk	15-24%	23%	12%	90.7%	58.7%	53.7%	99.4%	0.6%	6.8%
	25-49%	42%	18%	82.8%	72.5%	61.4%	99.2%	0.8%	5.2%
	50-74%	62%	16%	60.2%	88.8%	73.7%	98.8%	1.2%	5.5%
	75-84%	78%	6%	32.3%	97.5%	87.4%	98.9%	1.1%	2.6%
High Risk	≥ 85%	97%	6%	17.8%	99.7%	96.7%	100%	0%	1.2%
*Consensus based “clinically actionable” risk categories									

APPLICABILITY: This is a stage 4 clinical decision rule. It included a multicenter, prospective validation cohort and a single center, retrospective validation cohort. The lack of broad, prospective validation limits the study’s generalizability. The authors included “moderate” interrater reliability (kappa > 0.35) which would be considered “fair” by others. The kappa for the individual physical exam predictors (RLQ tenderness, rebound), that would be the most open to interpretation, were not presented. The equation may not be applicable to patients with suspected appendicitis on non-Children’s hospital settings.

Additionally, there is no tool available with which to calculate the score. The authors admit that the calculator is not intuitive and requires sophisticated calculations and suggest programming the pediatric appendicitis risk calculator into the electronic medical record.

Finally, the author’s consensus based (n=3) “clinically actionable” risk categories may not be acceptable to others. For example, low risk was classified as below 14%. Many would consider 14% an unacceptable miss rate. The high-risk classification would allow for a negative laparotomy rate that may not be acceptable for our surgical colleagues. Any change in the management strategy for appendicitis would require collaboration with our radiology and surgical colleagues.

AUTHOR’S CONCLUSION: “In this derivation and validation study, the pediatric appendicitis risk calculator was used to accurately quantify the risk of appendicitis among presenting to the PED with acute abdominal pain. Next steps include a prospective validation of the pediatric appendicitis risk calculator and an evaluation of how the pediatric appendicitis risk calculator may impact the care delivered.”

POTENTIAL IMPACT: The rule has the potential to decrease the rate of imaging in patients with suspected appendicitis. The decreased in imaging utilization must be balanced against the potential for missed appendicitis and an increase in the negative laparotomy rate. This is a stage IV clinical decision rule the requires further broad, prospective validation before it can be incorporate into clinical practice. In addition, there are a number of practical, implementation issues that need to be addressed.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

APPENDICITIS:
TIME TO APPENDECTOMY (2015)

In pediatric patients with CT confirmed appendicitis without evidence of perforation does an increased time from emergency department presentation to operative intervention result in an increase in appendiceal perforation confirmed by operative or biopsy findings?

Nicole Gerber, M.D., Michael Tunik, M.D.
November 2015

Bonadio W, Brazg J, Telt N, Pe M, Doss F, Dancy L, Alvarado M.

IMPACT OF IN-HOSPITAL TIMING TO APPENDECTOMY ON PERFORATION RATES IN CHILDREN WITH APPENDICITIS.

J Emerg Med. 2015 Nov;49(5):597-604.
PubMed ID: 26166465

STUDY DEFINITIONS	
POPULATION	Inclusion: Consecutive sample of patients < 18 years old with CT confirmed uncomplicated appendicitis. Defined as appendicitis without evidence of intraabdominal abscess, extra-luminal air, extra-luminal appendicolith, or focal defect in enhancing appendiceal wall. Exclusion: Perforated appendicitis on CT scan, no CT obtained Setting: Single, urban pediatric ED. 1/2010– 1/2014
INTERVENTION	Appendectomy > 9 hours from ED presentation (Defined as Time delay)
CONTROL	Appendectomy ≤ 9 hours from ED presentation (Defined as No/Less delay)
OUTCOME	Primary Outcome: Rate of perforation confirmed by operative or biopsy findings Secondary Outcomes: Length of hospital stay Number of XRAYS performed as an inpatient
DESIGN	Observational: Prospective Cohort Study

ARE THE RESULTS VALID? (COHORT STUDY)	
DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	Yes. There were no statistically significant differences between the groups in regard to gender, WBC count and symptom duration. There were statistically significant differences for age, fever, presence of an appendicolith and delay in hours from ED presentation to appendectomy. A regression analysis was completed to adjust for between group differences.
Were the circumstances and methods for detecting the outcome similar?	Yes. In all cases, the patients started with CT confirmation of uncomplicated appendicitis (as defined by criteria previously found to be both sensitive and specific for perforation). The outcome of perforation was assessed by either the operative or pathology report. There was no assessment of of agreement between the two methods.
Was follow-up sufficiently complete?	Yes. The patients with CT evidence of uncomplicated appendicitis went to the OR for appendectomy. The outcome was evaluated at that time.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

N = 404 with CT (+) for Appendicitis
No perforation: 248/404 = 61.3%
Perforation: 156/404 = 38.6%
Perforation after initial no perforation 54/248 = 21.7%
Total perforation = (156 + 54)/404 = 52%

ED TO OR	N	PERFORATION (%)
< 9 hours	30	0/30 (0%)
9-24 hours	176	37/176 (21%)
> 24 hours	42	17/42 (41%)

LOGISTIC REGRESSION	
PREDICTOR	ADJUSTED ODDS RATIO (95% CI)
Mean time ED to OR	1.10 (1.04, 1.16)*
Appendicolith	5.47 (2.65, 11.31)
Fever	3.92 (1.73, 8.91)
Mean age	1.05 (0.95, 1.16)
*The odds of developing perforation increased by 1.10 for each hour delay from ED presentation to OR	
At 8 hours OR = 2.05, 95% CI (1.00, 3.10) At 16 hours OR = 4.22, 95% CI (3.17, 5.27) At 24 hours OR = 8.67, 95% CI (7.62, 9.72)	

Pre-ED symptom duration ≥ 2 days bordered on significant (p=0.06) in the univariate analysis (Table 1). This has previously been associated with perforation, but was not included in the logistic regression analysis

HOW PRECISE IS THE ESTIMATE OF THE RISK?

For the primary outcome, the 95% confidence interval for the odds ratio is 1.04-1.16. As the interval does not include 1, it represents a statistically significant difference

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Yes. The patient population at Maimonides Medical Center is generally like our patient population at Bellevue Hospital. However, there was a high rate of perforated appendicitis on their initial CT scan (38.6%) suggesting that their population may be sicker or present later.
Was follow-up sufficiently long?	Yes. Although they did not specifically comment that all the patients were able to be followed for the duration of their hospital course, data was available on their main outcome, perforation at operative or biopsy findings.
Is the exposure similar to what might occur in my patient?	Yes. The exposure is a time delay > 9 hours. Depending on when a patient presents to the Bellevue ED, they might have a delay from ED presentation to OR of longer than 9 hours particularly if an equivocal ultrasound then requires a CT scan.
What is the magnitude of the risk?	The magnitude of the risk of perforation on operative or biopsy findings for time from ED presentation to operative intervention is 1.10, 95% CI (1.04-1.16). The odds of developing perforation increased by 1.10 for each hour delay from ED presentation to laparotomy. This is a relatively small increase in risk when compared to the other independent predictors of fever (Odds Ratio 3.92) and presence of an appendicolith (Odds Ratio 5.47) yet it is the only variable that is potentially modifiable. The odds ratio at the 24-hour mark is 8.67 exceeding that of fever and presence of an appendicolith.
Are there any benefits that are known to be associated with exposure?	Potential benefits with delay in time from ED presentation to appendectomy include, having a more senior surgeon available to perform the operation and having the surgeon/ anesthesiologist be more well rested if they did not have to be called in during the night time.

CLINICAL BOTTOM LINE

BACKGROUND: In the past, surgery for acute appendicitis was viewed as emergent requiring immediate appendectomy due to risk of perforation its complications. Recent literature has not shown a consistent increase in perforation rates with delayed appendectomy, and as such, combined with the benefits to the surgeon and potential benefits to the patient; the standard of care is currently to perform appendectomy on an urgent rather than emergent basis. However, studies are limited and this is still an area that requires additional research.

CLINICAL QUESTION: In pediatric patients with CT confirmed appendicitis without evidence of perforation does an increased time from emergency department presentation to operative intervention result in an increase in appendiceal perforation confirmed by operative or biopsy findings?

DESIGN/VALIDITY: This was an observational prospective cohort study conducted via retrospective chart review. The study included 404 patients with a CT scan indicating appendicitis of which 38.6% were perforated. Patients with CT confirmed non-perforated appendicitis had data collected on potential risk factors for perforation including time to appendectomy. Logistic regression was conducted to explore the independent effect of each risk factor on subsequent perforation.

PRIMARY RESULTS: The authors report an increased risk of perforation in patients waiting for appendectomy more than 9 hours after ED presentation. The logistic regression analysis resulted in an adjusted odds ratio of 1.10, 95% CI (1.04, 1.16) indicating that the odds of developing perforation increased by 1.10 for each hour delay from ED presentation to appendectomy. There was a “dose/response” relationship with a longer time to appendectomy resulting in higher rates of perforation. The presence of fever and an appendicolith were also independent predictors of subsequent perforation. In addition, an increased time from ED presentation to appendectomy resulted in an increase in inpatient length of stay and the number of imaging studies obtained.

There are several concerns with the presented results. In prior studies, a delay from symptom onset to presentation has been associated with a higher perforation rate. The authors reported time from symptom onset to ED presentation as a categorical variable (< 2 days or ≥ 2 days) and not a continuous variable. Although time from symptom onset to ED presentation closely approached significance in the univariable analysis ($p = 0.06$), it was not included in the logistic regression analysis. Another concern is the way in which the authors analyze the variable of time to appendectomy. The authors appear to analyze the effect of time in a linear fashion. They report an odds ratio at 8 hours of 2.05 yet there were no subsequent perforations in patients with a time of less than 9 hours from ED presentation (Figure 3).

APPLICABILITY: The study patients presented to a single center and the initial perforation rate of 39% is higher than what is typically documented in the literature, which is a rate closer to 20%. In addition, if patients who had perforation at appendectomy are included, then greater than 50% of the study patients had a perforated appendix. This may be the result of patients with an ultrasound diagnosis of appendicitis going for an appendectomy with a prior CT scan. However, this suggests that their population is not generalizable to all patients presenting with suspected appendicitis.

AUTHOR'S CONCLUSIONS: "Increasing in-hospital time delay from ED presentation to OR appendectomy is associated with increased risk for developing appendiceal perforation in children who present with CT documented uncomplicated appendicitis. Risk is approximately six-fold greater in those with delay >9 h vs. #9 h. Antibiotic therapy does not reliably prevent progression of the disease. Appendectomy should be considered an urgent procedure to maximize outcomes and prevent complications caused by appendix perforation."

POTENTIAL IMPACT: Given the number of limitations discussed above, larger multicenter studies may be needed before this data can be used to encourage pediatric surgeons to a return to the time when appendectomy is considered an emergent surgical procedure.

SEE ALSO:

Serres SK, Cameron DB, Glass CC, Graham DA, Zurakowski D, Karki M, Anandalwar SP, Rangel SJ. Time to Appendectomy and Risk of Complicated Appendicitis and Adverse Outcomes in Children JAMA Pediatr. 2017 Jun 19. [Epub ahead of print], PubMed ID: 28628705

This multicenter study involving 2,429 children concluded that a "Delay of appendectomy within 24 hours of presentation was not associated with increased risk of complicated appendicitis or adverse outcomes. These results support the premise that appendectomy can be safely performed as an urgent rather than emergency procedure."

APPENDICITIS:
TIME TO APPENDECTOMY (2017)

In pediatric patients with appendicitis who undergo an appendectomy less than 24 hours after ED presentation, is a longer time to appendectomy associated with an increased risk of complicated appendicitis and post-operative adverse events?

Michael Mojica, MD
July 2018

Serres SK, Cameron DB, Glass CC, Graham DA, Zurakowski D, Karki M, Anandalwar SP, Rangel SJ.

TIME TO APPENDECTOMY AND RISK OF COMPLICATED APPENDICITIS AND ADVERSE OUTCOMES IN CHILDREN.

JAMA Pediatr. 2017 Aug 1;171(8):740-746.
PubMed ID: 28628705

STUDY DEFINITIONS	
POPULATION	Inclusion: < 18 years, appendectomy for suspected appendicitis Exclusion: 1.Missing data: Time-point, operative report or pathology report 2.Transferred patients 3.Interval appendectomy 4.Without appendicitis on final pathology report 5.CT scan obtained as part of the evaluation for appendicitis 6.Time to appendectomy > 95th percentile for site (> 24 hours) 7.Sites enrolling < 40 patients Setting: 29 Children's Hospitals, 1/2013-12/2014 American College of Surgeons Pediatric National Quality Improvement Program (NSQIP) database
EXPOSURE/ NO EXPOSURE	Time to Appendectomy (TTA): From ED registration to operative incision 1.Continuous; Across all hospitals 2.Categorical: Early and late compared to the median at each site
OUTCOME	Primary Outcome: Complicated appendicitis based on operative note review 1.Visible hole in the appendix 2.Diffuse fibrino-purulent exudate throughout the peritoneal cavity 3.Intra-abdominal abscess 4.Fecalith in the peritoneal cavity Secondary Outcomes: 1.Length of stay 2.Rate of postoperative adverse events: a. Incisional surgical site infections b. Organ space surgical site infections 3.Percutaneous drainage procedure required 4.Unplanned re-operation 5.Hospital revisits to ED or outpatient
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	No. Patients in the late group were more likely to be female and have public health insurance) than those in the early group (Table 1). Multiple regression was used to assess the independent effects of predictors and potential confounders. Time from symptom onset to ED presentation and the presence or absence of complicated appendicitis on ultrasound were not included in the analysis.
Were the circumstances and methods for detecting the outcome similar?	Yes. Standardized procedures were used to maintain the quality of the database and to abstract data. However, it is unclear if operative reports were not standardized at each site.
Was follow-up sufficiently complete?	Yes. The primary outcome, complicated appendicitis was assessed for all patients and was based on the operative report. Of the secondary outcomes, it is unclear how hospital revisits were assessed.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

n = 2,429 children
n = 23 hospitals (6 sites excluded for enrolling < 40 patients), mean = 90 patients/site IQR 57-146
Male: 60.4%
Median age: 10 years, IQR 8-13 years

Median Time to Appendectomy: 7.4 hours, IQR 4.9-12.9 hours, Hospital range: 5.0-19.2 hours
Late group was significantly more likely to be female and have public health insurance

Complicated Appendicitis: 574/2429 (23.6%), Hospital range: 5.2, 51.1%
Complicated group was more likely to be female, Hispanic and have public health insurance

PREDICTORS OF COMPLICATED APPENDICITIS

	Odds Ratio (95% CI)
Time to Appendectomy (univariable)	1.00 (0.97, 1.02) per hour increase
Time to Appendectomy (multivariable)	0.99 (0.97, 1.02) per hour increase
Younger Age (7 years of age)	2.59 (1.97, 3.41)
Younger Age (8-12 years of age)	1.60 (1.25, 2.06)
Female	1.56 (1.20, 2.01)
Hispanic ethnicity	1.56 (1.20, 2.01)
GREEN = Statistically Significant, RED = Not Statistically Significant	

Odds of complicated disease (Late/Early): Hospital range 0.39-9.63 (Figure 3)
There was a statistically significant association between time to appendectomy and complicated appendicitis at 2 of the 23 study sites. 1 site had an increased risk of complicated appendicitis (OR 9.63 (0.88, 86.7)) and the 2nd site had a decreased risk in the late group (OR 0.47, (0.23, 0.93)).

ADVERSE EVENTS: ASSOCIATION WITH TIME TO APPENDECTOMY

PREDICTOR (OVERALL COHORT RATE)	ODDS RATIO (95% CI) PER HOUR INCREASE
Length of Stay (Median 2 days, IQR 2-4 days)	0.06 days (0.03, 0.08)
Incisional surgical site infection (1.0%)	0.96 (0.88, 1.04)
Organ Space surgical site infection (2.8%)	1.00 (0.96, 1.05)
Percutaneous drainage (2.6%)	1.02 (0.97, 1.07)
Unplanned re-operation (1.2%)	1.00 (0.93, 1.07)
Hospital revisit (8.9%)	1.01 (0.99, 1.04)
GREEN = Statistically Significant, RED = Not Statistically Significant	

HOW PRECISE IS THE ESTIMATE OF THE RISK?

Given the large sample size, confidence intervals for the odds ratios above are narrow

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	The only patient data provided (Table 1, 2) are age, sex, race and insurance status. Given that the study included 23 children's hospitals, it is like that our patients are similar. Hispanic race was associated with an increased risk of complicated appendicitis and our Bellevue population is predominantly Hispanic. There was a 6.3% (428/6,767) negative laparotomy rate.
Was follow-up sufficiently long?	Yes. The primary outcome was the rate of complicated appendicitis on appendectomy.
Is the exposure similar to what might occur in my patient?	Unclear. Unsure what our time to appendectomy is or what our appendectomy complication rate is. It is unlikely that our pediatric surgery group would accept a 6.3% negative laparotomy rate.
What is the magnitude of the risk?	There was not an increased risk of complicated appendicitis associated with time to appendectomy. Younger age (7 years of age OR 2.59, 8-12 years OR 1.60 , female sex (OR 1.56) and Hispanic race (OR 1.56) were associated with an increased risk of complicated appendicitis.
Are there any benefits that offset the risks associated with exposure?	Potential benefits with delay in time from ED presentation to appendectomy include: having a more senior surgeon available to perform the operation and having the surgeon and anesthesiologist be more well rested if they did not have to be called in during the night time.

CLINICAL BOTTOM LINE

BACKGROUND: In the past, surgery for acute appendicitis was viewed as emergent requiring immediate appendectomy due to the risk of perforation and it's complications. Recent literature has had conflicting results regarding an increase in perforation rates associated with a delay in appendectomy. Current practice is to perform appendectomy on an urgent rather than emergent basis due to the potential benefits of delay to the surgeon and patients.

CLINICAL QUESTION: In pediatric patients with appendicitis who undergo an appendectomy less than 24 hours after ED presentation is a longer time to appendectomy associated with an increased risk of complicated appendicitis and post-operative adverse events?

DESIGN/RISK OF BIAS: The was a retrospective cohort study using a multicenter pediatric surgical database (23 children's hospitals). 2,429 patients undergoing appendectomy within 24 hours of ED presentation were included. Patients receiving a CT scan were excluded from the analysis. The primary predictor of interest was time to appendectomy (TTA) defined as time from ED presentation surgical incision. TTA was dichotomized as early of late based on the individual hospital median time to appendectomy. The primary outcome was complicated appendicitis based on the operative note description of the appendix and abdominal cavity.

Time from symptom onset to ED presentation, the presence or absence of complicated appendicitis on ultrasound prior to appendectomy and antibiotic timing were not included in the analysis. It is also unclear what prompted the decision to operate. Most patients likely underwent appendectomy based on a ultrasound that was consistent with appendicitis. How equivocal ultrasounds were handled is not addressed. Some patients could have gone to the OR based on exam findings alone and some after serial exams while admitted for observation.

PRIMARY RESULTS: The median time to appendectomy was 7.4 hours IQR (4.9-12.9 hours). The hospital range for TTA was 5.0-19.2 hours. The late group was significantly more likely to be female sex and have public health insurance. Complicated appendicitis occurred in 23.6% (574/2429) of patients (23.6%), The hospital range was 5.2-51.1%. The complicated group was more likely to be female, of Hispanic race and have public health insurance.

PREDICTORS OF COMPLICATED APPENDICITIS	
	Odds Ratio (95% CI)
Time to Appendectomy (univariable, fixed)	1.00 (0.97, 1.02) per hour increase
Time to Appendectomy (multivariable)	0.99 (0.97, 1.02) per hour increase
Younger Age (7 years of age)	2.59 (1.97, 3.41)
Younger Age (8-12 years of age)	1.60 (1.25, 2.06)
Female	1.56 (1.20, 2.01)
Hispanic ethnicity	1.56 (1.20, 2.01)
GREEN = Statistically Significant, RED = Not Statistically Significant	

Time to appendectomy was not an independent predictor of complicated appendicitis. Young age (7 years and 8-12 years), female sex and Hispanic ethnicity were independent predictors of complicated appendicitis (Table above).

Time to appendicitis was associated with an increased length of stay but not in an increase in any of the other post-operative adverse events (Table below).

ADVERSE EVENTS: ASSOCIATION WITH TIME TO APPENDECTOMY	
PREDICTOR (OVERALL COHORT RATE)	ODDS RATIO (95% CI) PER HOUR INCREASE
Length of Stay (Median 2 days, IQR 2-4 days)	0.06 days (0.03, 0.08)
Incisional surgical site infection (1.0%)	0.96 (0.88, 1.04)
Organ Space surgical site infection (2.8%)	1.00 (0.96, 1.05)
Percutaneous drainage (2.6%)	1.02 (0.97, 1.07)
Unplanned re-operation (1.2%)	1.00 (0.93, 1.07)
Hospital revisit (8.9%)	1.01 (0.99, 1.04)
GREEN = Statistically Significant, RED = Not Statistically Significant	

APPLICABILITY: The only patient data provided (Table1, 2) are: age, sex, race and insurance status. Given that the study included 23 children's hospitals, it is like that our patients are similar. Hispanic race was associated with an increased risk of complicated appendicitis and our Bellevue population is predominantly Hispanic. It is unclear if the study's result could be generalized to non-children's hospital settings. There was a 6.3% (428/6,767) negative laparotomy rate. It is doubtful that are pediatric surgery group would accept a 6.3% this rate. The range in a hospital's rate of complicated appendicitis was 5.2-51.1%. It is unclear if this is related to difference in the patient population or institutional practice.

AUTHOR'S CONCLUSION: "Despite these limitations, we conclude that delay of appendectomy does not increase the risk of complicated appendicitis when performed within 24 hours of presentation. In the context of contemporary clinical practice, these data support the premise that treating appendicitis as an urgent (rather than emergency) condition is safe and that delay of appendectomy until the following day in children presenting after hours is an acceptable practice. These findings may have important implications for many hospitals at which performing an appendectomy at night poses significant logistical and fiscal challenges. The ultimate decision surrounding timing of appendectomy should balance the benefits of a timely intervention (e.g., potentially lower hospital cost, length of stay, and lost days from school and work on behalf of the patient and their family) against a hospital's available resources but should not be influenced by concern for clinically relevant disease progression if it can be performed in a reasonable time frame."

POTENTIAL IMPACT: Time to appendectomy was not associated with an increased risk of complicated appendicitis or any of the post-operative complications with the exception of an increased length of stay. It is likely that appendectomy can be performed on an urgent rather than an emergent basis as is currently our pediatric surgeon's practice. However, important confounders such as the duration of symptoms prior to ED presentation, presence of peritoneal signs on examination and evidence of perforation or appendiceal diameter on imaging prior to appendectomy were not included in the analysis. Younger patients (?non-specific symptoms, difficulty in interpreting physical findings) and female sex (? broader differential diagnosis) and Hispanic race (?) were independently associated with a higher rate of complicated appendicitis. This should be considered when caring for these patients.

INTUSSUSCEPTION:
3-VIEW ABDOMINAL XRAY (PROSPECTIVE)

In children with suspected intussusception what are the test characteristics of a 3-view abdominal XRAY (supine, prone, and left lateral decubitus) when compared to air enema, operative findings or clinical follow-up for identifying those with and without intussusception?

Cindy Roskind, M.D., Michael Mojica, M.D.

April 2012

Roskind CG, Kamdar G, Ruzal-Shapiro CB, Bennett JE, Dayan PS.

ACCURACY OF PLAIN RADIOGRAPHS TO EXCLUDE THE DIAGNOSIS OF INTUSSUSCEPTION

Pediatr Emerg Care. 2012 Sep;28(9):855-8.
PubMed ID: 22929143

STUDY DEFINITIONS	
POPULATION	Inclusion: 3- 36 months. underwent 3-view abdominal radiography for intussusception (standard practice at the study institution) Exclusion: Previous abdominal surgery, including gastrostomy, jejunostomy tube Setting: Single Children's Hospital ED, 5/2004-5/2006
TESTS	A. Negative XRAY: Air in the ascending colon on all 3 views OR ≥ 2 views 1. Air noted in bowel positioned parallel and adjacent to the right lateral abdominal wall in continuity with the hepatic flexure with or without clearly delineated haustral markings OR 2. Air parallel and adjacent to the right lateral abdominal wall with clearly defined haustral markings. Hepatic Flexure: Fold of large bowel between the ascending colon and the transverse colon immediately adjacent to the liver. Haustral Markings: Folds that did not traverse the width of the bowel completely, differentiating them from the valvulae connivente of the small bowel. B. Negative XRAY: Air in the transverse colon on the supine view. Air lying below the greater curvature of the stomach, extending from the liver edge on the right to the splenic flexure on the left. C. Negative XRAY: Air or stool in the cecum D. Negative XRAY: No evidence of small bowel obstruction, target sign, meniscus or (crescent) sign XRAYs reviewed by single pediatric radiologist not involved in patient's care
REFERENCE STANDARD	Intussusception Yes: Positive abdominal ultrasound, air enema, or operative procedure. intussusception No: Negative ultrasound, air enema, operative procedure, or improvement in clinical course (telephone follow-up at 1 week or review of inpatient records if hospitalized).
OUTCOME	Test Characteristics of A, B, C and D above
DESIGN	Observational: Prospective cross section study

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. Patients were enrolled if they had a 3 view AXR for the evaluation of intussusceptions. 15% of the study population had intussusception.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The reference standards used were abdominal ultrasound (performed by pediatric radiology), air enema, surgical operative note, or clinical follow up performed at one week.
Were those interpreting the test and reference standard blind to the other results?	Yes. The radiographs were interpreted later by blinded radiologists who had no knowledge of whether other radiologic studies had been performed, their results or patient outcomes.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	No. The real-time interpretation of the radiographs influenced whether ultrasound or enema were obtained. However, the blinded re-read of the radiograph was done at a later date solely for the purposes of the study and did not influence clinical decision making. All participants received a reference standard, though in many cases, it was clinical follow up.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 128, 19 (14.8%) with intussusception
Median age: 17 months, IQR (9.1, 26), male 60%

ABD XRAY (AIR ON ALL 3 VIEWS (TABLE 2)

	INTUSSUSCEPTION		
	YES	NO	
POSITIVE: AIR ON < 3 VIEW	19	90	109
NEGATIVE: AIR ON 3 VIEWS	0	19	19
	19	109	128

Prevalence: 19/128 = 14.8%, 95% CI (9.2, 22.2%)
Sensitivity: 19/19 = 100%, 95% CI (79.1, 100%)
Specificity: 19/109 = 17.4%, 95% CI (11.1, 26.1%)
Predictive Value Positive Test: 19/109 = 17.4%, 95% CI (16.2, 18.7%)
Predictive Value Negative Test: 19/19 = 100%, 95% CI (79.1, 100%)
Likelihood Ratio Positive Test: (19/19)/(90/109) = 1.2, 95% CI (1.1, 1.3)
Likelihood Ratio Negative Test: (0/19)/(19/109) = 0

ABD XRAY (AIR ON ≥ 2 VIEWS (TABLE 3)

	INTUSSUSCEPTION		
	YES	NO	
POSITIVE: AIR ON < 2 VIEW	17	60	77
NEGATIVE: AIR ON ≥ 2 VIEWS	2	49	51
	19	109	128

Prevalence: 19/128 = 14.8%, 95% CI (9.2, 22.2%)
Sensitivity: 17/19 = 89.5%, 95% CI (75.7, 100%)
Specificity: 49/109 = 45.0%, 95% CI (35.6, 54.3%)
Predictive Value Positive Test: 17/77 = 22.1%, 95% CI (18.4, 26.3%)
Predictive Value Negative Test: 49/52 = 96.1, 95% CI (90.8, 100)
Likelihood Ratio Positive Test: (17/19)/(60/109) = 1.6, 95% CI (1.3, 2.0)
Likelihood Ratio Negative Test: (2/19)/(49/109) = 0.23 (0.06, 0.88)

<u>Abdominal XRAY (Air in Transverse Colon (Table 4))</u>
Sensitivity: 84%
Specificity: 63.3%,
Predictive Value Positive Test: 28.6%
Predictive Value Negative Test: 95.8%,

Likelihood Ratio Positive Test: 2.3,
Likelihood Ratio Negative Test: 0.09

OTHER XRAY FINDINGS	SENSITIVITY
Air/stool in the cecum	68.4%, (SP 70.6%)
Soft tissue mass	26.3%
Small bowel obstruction	15.8%
Target sign	0%
Meniscus (crescent) sign	0%

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	The radiographs in this study were interpreted by one experienced pediatric radiologist. Though specific criteria were applied, the test characteristics may be lower when interpreted by radiology residents or EM physicians. A measure of inter-rater reliability (kappa statistic) or a comparison of the study radiologist's interpretation to the clinical radiologist's interpretation would have been helpful.
Are the study results applicable to the patients in my practice?	Yes. Our patients are similar to the children enrolled in the study (tertiary care, urban PED with relatively low rates of intussusception). The three-view abdominal radiograph may be most helpful at night as a screening tool when ultrasound is not readily available.
Will the test results change my management strategy?	In patients with low pretest probability of intussusception, clinicians may consider using the 3 view abdominal radiographs as a screening test for intussusception. However, the limitations of this study (small size, lack of inter-rater reliability) preclude the use of 3-view abdominal XRAY as a gold standard for diagnosis. For patients with moderate to high risk of disease, clinicians should still consider obtaining other diagnostic tests.
Will patients be better off as a result of the test?	Patients at low risk of intussusception may benefit from the use of abdominal XRAY as a screening tool (easy to perform, inexpensive, low radiation dose) prior to obtaining more resource requiring studies such as ultrasound and enema.

CLINICAL BOTTOM LINE

EDITORS NOTE: This PEMCAR was initially written by the study's principle author for a fellow evidence based medicine course. To avoid potential bias, the PEMCAR underwent a complete review and revision independently by a second faculty reviewer.

BACKGROUND: Pediatric patients who present to the ED with a clinical picture concerning for intussusception represent a diagnostic dilemma for ED physicians. Currently the gold standard to diagnose intussusception is either ultrasound or air enema. These studies, although accurate, require specialized pediatric radiology resources and are not without cost and risk (transport to and from radiology, risk of perforation and radiation exposure from air enema). It has been suggested in previous studies that the presence of air in the ascending colon on AXR can effectively rule out intussusception.

CLINICAL QUESTION: In children with suspected intussusception what are the test characteristics of a 3-view abdominal XRAY (supine, prone, and left lateral decubitus) when compared to air enema, operative findings or clinical follow-up for identifying those with and without intussusception?

DESIGN/RISK OF BIAS: This prospective study analyzed the ability of 3-View AXR (supine, prone, and left lateral decubitus) to accurately rule out the diagnosis of intussusception in patients with low pretest probability of disease. The study included 128 patients with suspected intussusception for which a 3-view abdominal XRAY was obtained. 19/128 (14.8%) of the patients had intussusception. This was a well-designed study with some important limitations with the test characteristics (low specificity, wide confidence intervals) and single pediatric radiologist interpretation without an assessment of inter-rater reliability).

PRIMARY RESULTS: In this study, the presence of air in the ascending colon on 2 of the 3 views reduced the likelihood of intussusception, while presence of air on all 3 views ruled out all cases of intussusception. In a population with 14.8% probability of intussusception, the presence of air on < 3 views resulted in a 17.4% (predictive value of positive test) probability of intussusception and the presence of air on all 3 views resulted in a 0% (1 – predictive value of a negative test) probability of intussusception. It is important to note that only 14.8% (19/128) of patients had air identified on all 3 views. The table below illustrates the tradeoff between sensitivity and specificity. In going from left to right in the table the criteria for a negative test becomes less stringent. As the criteria become less stringent the sensitivity decreases and the specificity increases

	AIR ON ALL 3 VIEWS	AIR ON ≥ 2 VIEWS	AIR TRANSVERSE COLON
Prevalence	14.8% (9.2, 22.2%)	14.8%, (9.2, 22.2%)	14.8%, (9.2, 22.2%)
Sensitivity	100% (79.1, 100%)	89.5% (75.7, 100%)	84.2 (60.4, 96.6%)
Specificity	17.4% (11.1, 26.1%)	45.0% (35.6, 54.3%)	63.3 (53.5, 72.3%)
Predictive value (+)	17.4% (16.2, 18.7%)	22.1% (18.4, 26.3%)	28.6 (22.6, 35.4%)
Predictive value (-)	100% (79.1, 100%)	96.1 (90.8, 100)	95.8% (89.0, 98.5%)
Likelihood ratio (+)	1.2 (1.1, 1.3)	1.6 (1.3, 2.0)	2.3 (1.7, 3.1)
Likelihood ratio (-)	0	0.23 (0.06, 0.88)	0.25 (0.09, 0.7)

APPLICABILITY: The study's results are likely applicable to those patients with suspected intussusception meeting the study's inclusion and exclusion materials. The primary limitation in generalizing the study's results is that a single very experience pediatric radiologist who was not involved in the clinical care of the patient interpreted all XRAY's. No measure of inter-rater reliability was presented. It would have been helpful to compare the study radiologist's interpretation to that of the clinical radiologist who read the studies initially.

AUTHOR'S CONCLUSION: "The 3-view abdominal radiograph series, using specific criteria, can decrease and potentially exclude the diagnosis of ileocolic intussusception. Trade-offs in sensitivity and specificity do exist depending on the radiographic criteria used. When clinical suspicion for intussusception is low, the presence of specific criterion noted on a 3-view abdominal radiograph series may obviate the need for further studies."

POTENTIAL IMPACT: This study's results may be most helpful in settings in which ultrasound for intussusception is not available. In general, ultrasound is operator dependent. Our pediatric radiologists have faith in the reliability of ultrasound performed by radiology trainees and studies of point of care ultrasound by pediatric emergency medicine physicians have demonstrated reasonable test characteristics.

INTUSSUSCEPTION:
3-VIEW ABDOMINAL XRAY (RETROSPECTIVE)

In children presenting with a clinical picture suggestive of intussusception, how accurate is the presence of air in the ascending colon on all 3 views or on ≥ 2 views of abdominal XRAYs (Supine, Prone, and Lateral Decubitus views) at distinguishing between those with and without intussusception?

Eric Weinberg, M.D., Adriana Manikian M.D.
January 2008

Roskind CG, Ruzal-Shapiro CB, Dowd EK, Dayan PS.

TEST CHARACTERISTICS OF
THE 3-VIEW ABDOMINAL RADIOGRAPH SERIES
IN THE DIAGNOSIS OF INTUSSUSCEPTION.

Pediatr Emerg Care. 2007 Nov;23(11):785-9.
PubMed ID: 18007208

STUDY DEFINITIONS	
POPULATION	Inclusion: 3 months-3 years, 3-view abdominal radiography for intussusception Exclusion: Prior abdominal surgery, past illnesses with an underlying abnormal bowel gas pattern or a high likelihood of obstruction (e.g. necrotizing enterocolitis, cystic fibrosis, chronic mal-absorptive syndromes), previous intussusception. Setting: Single Children's Hospital ED, 1/1997-12/2002.
TEST	3 View Abdominal XRAY: Supine, Prone, and Lateral Decubitus. Air visualized in the ascending colon on each of the 3 views or ≥ 2 views 1. Air noted in bowel positioned parallel and adjacent to the right lateral abdominal wall in continuity with the hepatic flexure with or without clearly delineated haustral markings OR 2. Air parallel and adjacent to the right lateral abdominal wall with clearly defined haustral markings. Hepatic Flexure: Fold of large bowel between ascending colon and transverse colon immediately adjacent to the liver. Haustral Markings: Folds that do not traverse the width of the bowel completely, differentiating them from the valvulae connivente of the small bowel.
REFERENCE STANDARD	Radiographic Outcome: Ultrasound or an air enema report with a clear description of the presence or absence of intussusception. Surgery Outcome: Review of medical records and operative notes. Clinical Outcome: Telephone follow-up within 14 days of ED discharge, review of medical records. Only If no definitive radiographic study or operative procedure performed.
OUTCOME	Test characteristics of a 3-view abdominal radiograph series when: 1. All 3 views had air in the ascending colon. 2. ≥ 2 views had air in the ascending colon.
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. Patients were entered in the study if there was clinical suspicion of intussusception and a 3-view abdominal XRAY was ordered. 15% of patients had intussusception.
Did investigators compare the test to an appropriate, independent reference standard?	The reference standard was based on 1 of 3 criteria: “definitive radiography” (Ultrasound or air enema), surgical operative note, or clinical follow up. It is likely that a negative sonogram precluded the use of an air enema.
Were those interpreting the test and reference standard blind to the other results?	A single attending pediatric radiologist with 18 years of experience reviewed all radiographs, masked to the patient’s clinical data and presence or absence of intussusception. The abdominal XRAY was done prior to confirmatory studies so it is likely that the initial radiologist interpreted the abdominal XRAY prior to the results of other studies were available.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	No. 3 outcomes measures were used. Radiologic, surgical and clinical confirmation. Because of the retrospective design, it was likely that the results of the 3-view abdominal XRAY influenced the decision to perform an ultrasound or air enema so there is a possibility of verification or workup bias.

WHAT ARE THE RESULTS?

N = 179
Intussusception: 27/179 = 15.1% (10.2, 21.2%)

Reference Standards
Definitive Study: 80/179 (44.7%)
Clinical follow up: 99/179 (56.3%)

AIR IN ASCENDING COLON ON 3 VIEWS (TABLE 3)

	INTUSSUSCEPTION		
	YES	NO	
POSITIVE: AIR ON < 3 VIEW	27	124	151
NEGATIVE: AIR ON 3 VIEWS	0	28	28
	27	152	179

Prevalence: 27/179 = 15.1% (10.2, 21.2%)
Sensitivity: 27/27 = 100%, 95% CI (87, 00%)
Specificity: 28/152 = 18%, 95% CI (12, 25%)
Predictive Value Negative Test: 28/28 = 100%, 95% CI (98, 100%)
Predictive Value Positive Test: 27/151 = 17.8%, 95% CI (12.3, 25.1%)
Likelihood Ratio Negative Test: (0/27)/(28/152) = 0, 95% CI (0.01, 1.53)
Likelihood Ratio Positive Test: (27/27)/(124/152) = 1.2, 95% CI (1.1,1.3)

AIR IN ASCENDING COLON ≥ 2 VIEWS (TABLE 2)

	INTUSSUSCEPTION		
	YES	NO	
POSITIVE: AIR ON < 2 VIEW	26	89	115
NEGATIVE: AIR ON ≥ 2 VIEWS	1	63	64
	27	152	179

Prevalence: 27/179 = 15.1%, 95% CI (10.2, 21.2%)
Sensitivity: 26/27 = 96%, 95% CI (89-100%)
Specificity: 63/152 = 41%, 95% CI (34, 49%)
Predictive Value Negative Test: 63/64 = 98%, 95% CI (95, 100%)
Predictive Value Positive Test: 26/115 = 22.6%, 95% CI (15.5, 31.5%)
Likelihood Ratio Negative Test: (1/27)/(63/152) = 0.09, 95% CI (0.01, 0.62)
Likelihood Ratio Positive Test: (26/27)/(89/152) = 1.6, 95% CI (1.4, 1.9)

The relatively small sample size leads to wide confidence intervals for the test characteristics.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Unlikely. The sensitivity and likelihood ratios achieved by this study have two main limiting factors when applied to clinical settings. The interpretation of the 3-View AXR required an experienced pediatric radiologist. In this study only one senior pediatric radiologist reviewed the XRAYS. The authors acknowledge that the sensitivity may be lower when interpreted by ED physicians or less experienced radiologists. It would have been helpful for a second radiologist to review a sample of the films to generate a measure of inter-relater reliability.
Are the study results applicable to the patients in my practice?	Yes. Our patients are similar to the patients in this study. Abdominal ultrasound is also available 24/7 at our institution so the utility of abdominal XRAYs is limited.
Will the test results change my management strategy?	The limits of this study (retrospective design, verification bias, low specificity, wide confidence intervals, need for pediatric radiologist interpretation,) prevent the implementation of 3-view AXR as an initial evaluation for intussusception. In setting in which ultrasound is not readily available XRAY has the potential to decrease confirmatory testing in those with a low pretest probability of disease.
Will patients be better off as a result of the test?	Potential Benefits: The 3-View AXR is easier and quicker to perform than ultrasound. Potential Risks: Until prospective studies are completed, it is possible that this modality is less accurate than ultrasound, resulting in possible missed diagnoses or overuse of confirmatory studies.

CLINICAL BOTTOM LINE

BACKGROUND: Pediatric patients who present to the ED with a clinical picture concerning for intussusception represent a diagnostic dilemma. Currently, the gold standard to diagnose intussusception is either ultrasound or air enema. These studies, although accurate, require specialized pediatric radiology resources and are not without cost and risk. It has been suggested that the presence of air in the ascending colon on AXR can effectively rule out intussusception.

CLINICAL QUESTION: In children presenting with a clinical picture suggestive of intussusception, how accurate is the presence of air in the ascending colon on all 3 views or on ≥ 2 views of abdominal XRAYs (Supine, Prone, and Lateral Decubitus views) at distinguishing between those with and without intussusception?

DESIGN/RISK OF BIAS: This retrospective cohort study analyzed the ability of air in the ascending colon on a three-view abdominal XRAY (prone, lateral decubitus and supine) to identify intussusception. It included 179 patients with suspected intussusception of which 27 (15.1%) had confirmatory evidence of intussusception. This was a well-designed study though with several important validity concerns must be addressed. This includes the possibility of verification bias (not all patients had radiologic or confirmatory studies and that no assessment of the inter-rater was assessed and the abdominal XRAY were interpreted by a single, senior pediatric radiologist potentially inflating the test characteristics presented.

PRIMARY RESULTS: The test characteristics of a 3-view abdominal XRAY with air in the ascending colon on either 3 views or ≥ 2 views are presented in the table below. The sensitivities of both approaches are high (3 views: 100% 95% CI (87-100%), ≥ 2 views 96%, 95% CI (89, 100%). However, the lower limits of the confidence intervals allow for the possibility of missing patients with intussusception. Air in the descending colon on 3 views, risk stratified a group with 15.1% prevalence of intussusception into a high-risk group (17.8% post-test probability of intussusception with air on less than 3 views) and a low risk group (0% post-test probability of intussusception with air on all 3 views). Air in the descending colon on ≥ 2 views, risk stratified a group with 15.1% prevalence of intussusception into a high-risk group (22.6% post-test probability of intussusception with air on less than 2 views) and a low risk group (2% post-test probability of intussusception with air on ≥ 2 views).

AIR IN THE ASCENDING COLON	3 VIEWS	≥ 2 VIEWS
Sensitivity	100% (87-100%)	96% (89-100%)
Specificity	18% (12-25%)	41% (34-49%)
Predictive Value of a Positive Test	17.8% (12.3, 25.1%)	22.6% (15.5, 31.5%)
Predictive Value of a Negative Test	100% (98-100%)	98% (95-100%)
Likelihood Ratio of a Positive Test	0 (0.01-1.53)	0.09 (0.01-0.62)
Likelihood Ratio of a Negative Test	1.2 (1.1,1.3)	1.6 (1.4, 1.9)

Very few patients are “ruled out” for intussusception using abdominal XRAY. Only 15.6% (28/179) of patients had air visible in the ascending colon on all three views and 35.8% (64/170) had air visible in the ascending colon on ≥ 2 views Therefore, the majority of the patients will still require additional studies.

APPLICABILITY: The study's results could likely be generalizable to most patients meeting its inclusion and exclusion criteria. The major applicability concern is the reproducibility of XRAY interpretation by lesser experienced and non-pediatric radiologists.

AUTHOR'S CONCLUSION: "Our data suggest that the presence of air in the ascending colon on 2 or 3 abdominal radiograph views, with specifically defined criteria, has the potential to substantially decrease the likelihood of or exclude intussusception for children seen in the ED. Further investigation into the test characteristics of the 3-view abdominal radiograph series and the reliability of the interpretation among different users for the criteria defined in this study is warranted. A single-center prospective cohort study evaluating the test characteristics of the 3-view radiograph in the diagnosis of intussusception is currently underway, as is a multicenter study that will consider measures of interrater reliability among radiologists."

POTENTIAL IMPACT: Suggestions to externally validate this study include a prospective analysis of the 2 and 3-view AXR in larger populations, and analysis of the inter-rater reliability of radiographic interpretation by radiologists with less experience and by non-pediatric radiologists. The accuracy of abdominal ultrasound has generally replaced the use of abdominal XRAYS as a screening tool for intussusception but there may some utility of abdominal XRAY in some settings in which ultrasound is not readily available.

SEE ALSO: Subsequent prospective study by the principle author.
LINK TO: **PROSPECTIVE STUDY IN THIS PEMCAR IBOOK**

Roskind CG, Kamdar G, Ruzal-Shapiro CB, Bennett JE, Dayan PS.
Accuracy of Plain Radiographs to Exclude the Diagnosis of Intussusception
Pediatr Emerg Care. 2012 Sep;28(9):855-8., PubMed ID: 22929143

INTUSSUSCEPTION: CLINICAL AND XRAY FINDINGS

In children less than 3 of age years presenting to an emergency department with suspected intussusception are signs, symptoms and abdominal XRAY findings when compared to abdominal ultrasonography accurate in identifying those with and without intussusception?

Joanne Agnant, M.D., Jeffrey Hom, M.D.

May 2011

Mendez D, Caviness AC, Ma L, Macias CC.

THE DIAGNOSTIC ACCURACY OF AN ABDOMINAL RADIOGRAPH WITH SIGNS AND SYMPTOMS OF INTUSSUSCEPTION.

Am J Emerg Med. 2012 Mar;30(3):426-31.
PubMed ID: 21447436

STUDY DEFINITIONS	
POPULATION	Inclusion: 0-36 months, signs and symptoms of intussusception (ICD9 Codes: lethargy, vomiting, abdominal pain, right upper quadrant (RUQ) mass, bloody stools, or abdominal distension), imaging (XRAY: 2 view: flat, upright), ultrasound or enema (contrast or air)) Exclusion: History prior surgery, bowel obstruction, intussusception Setting: Single Children's Hospital ED, 10/1999-10/2004
TEST	Structured data collection form: Clinical characteristics: Lethargy, vomiting, abdominal pain, bloody stools, abdominal distension, right upper quadrant mass Abdominal XRAY: classification from radiologist report Highly suggestive: ≥ 1 of soft tissue mass, bowel obstruction, visible intussusception, sparse large bowel gas pattern Moderately suggestive: nonspecific bowel gas pattern, no mass or obstruction Not suggestive: normal bowel gas pattern, no mass or obstruction Ultrasound: Radiologist report
REFERENCE STANDARD	Identification of intussusception by enema or at time of surgery
OUTCOME	Test characteristics
DESIGN	Observational: Retrospective cross-sectional study

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. The patients presented with multiple complaints, including abdominal pain, vomiting, and lethargy. Intussusception was one possible etiology of their complaints. The prevalence of intussusception in this sample was 1.9% (124/6,314) or 59% (124/201) of those who had imaging.
Did investigators compare the test to an appropriate, independent reference standard?	Unclear. The investigators stated that they would use intussusception diagnosed by enema or surgery as the reference standard though only 72% had one of these and clinical follow up of those who did not undergo the reference standard was not reported.
Were those interpreting the test and reference standard blind to the other results?	No. Interpretation of abdominal radiographs and ultrasound occurred prior to enema or operative intervention. Those performing the enema or operation were very likely aware of XRAY and ultrasound results but it is unlikely that this knowledge would influence interpretation of the reference standard.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	No. Every patient was not compared to the reference standard because patients with a negative radiography or ultrasound did not undergo surgery (proportion not reported) or enema (72%). It would have been unethical to perform the reference standard for all patients. Clinical follow up was not reported.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 201, 124 (62%) with intussusception
Abdominal XRAY obtained: 85%
Ultrasound obtained: 32%
Proportion with individual clinical findings: Not presented

	UNIVARIATE ODDS RATIO	MULTIVARIATE ADJUSTED OR
RUQ mass	8.9 (1.14, 69.47)	
Vomiting	2.54 (1.36, 4.76)	
Abdominal pain	2.45 (1.36. 4.40)	2.80 (1.34, 5.85)
Bloody stools	2.21 (0.92, 5.27)	2.75 (1.33, 5.69)
Lethargy	1.75 (0.90, 3.41)	2.70 (1.07, 6.81)
Abdominal distension	0.99 (0.31, 3.15)	

<u>Clinical Findings (Table 4)</u>
No single clinical finding had a sensitivity of > 88%
Highest sensitivity: Bloody stools: Sensitivity 87.6%, Specificity 23.7%
Highest specificity: RUQ mass: Sensitivity 10.5%, Specificity 98.7%

<u>Highly Suggestive Abdominal XRAY</u>
Sensitivity: 90.2%
Specificity: 63.4%
Likelihood Ratio (+) Test: (0.9)/(1-0.63) = 2.43
Likelihood Ratio (-) Test: (1-0.9)/(0.63) = 0.16

<u>Ultrasound</u>
Sensitivity: 97.2%
Specificity: 93.1%
Likelihood Ratio (+) Test: (0.97)/(1-0.93) = 13.86
Likelihood Ratio (-) Test: (1-0.97)/(0.93) = 0.03

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	The imaging studies were read by 12 pediatric radiology attendings. If a pediatric radiology attending is not available, the results may not be as sensitive. As this was a retrospective study, there was no kappa statistic for interrater agreement on either the radiographic or clinical findings.
Are the study results applicable to the patients in my practice?	Yes. The patient population studied in this article is similar to our patient population in respect to age, gender, and ethnicity. The authors did not offer further description of their population, i.e. chronic medical diseases, socioeconomic levels, etc.
Will the test results change my management strategy?	No. Abdominal ultrasound is available in our institution with relatively reliable accuracy.
Will patients be better off as a result of the test?	It may benefit the patient with signs, symptoms, and radiograph that is highly suggestive of intussusception. The provider may decide that the risk of delay is too high if ultrasound is not immediately available.

CLINICAL BOTTOM LINE

BACKGROUND: Pediatric patients who present to the ED with a clinical picture suggestive of intussusception represent a difficult diagnostic decision for ED physicians. Currently the gold standard to diagnose intussusception is either ultrasound or air enema. These studies, although accurate, present some logistical difficulties and are not without risk (transport to and from radiology, risk of perforation and radiation exposure from air enema).

CLINICAL QUESTION: In children less than 3 of age years presenting to an emergency department with suspected intussusception are signs, symptoms and abdominal XRAY findings when compared to abdominal ultrasonography accurate in identifying those with and without intussusception?

DESIGN/RISK OF BIAS: This is a retrospective, cross-sectional study of children at risk for intussusception that included 201 patients of which 124 (62%) had intussusception. The objective was to compare the diagnostic accuracy of abdominal ultrasound to that of a highly suggestive abdominal radiograph combined with signs and symptoms of intussusception. The primary validity confirm is that not all patients underwent the reference standard (verification bias) and there was no discussion of clinical follow up for those not having the reference standard. There are additional concerns that are inherent to retrospective data collection.

PRIMARY RESULTS: The authors found that the combination of a highly suggestive abdominal radiograph, abdominal pain, lethargy, and vomiting was highly specific (95%) for intussusception, and was comparable to that of an ultrasound (93%). No individual clinical finding was as accurate as abdominal ultrasound.

The authors suggest that the combination of a highly suggestive abdominal radiograph with abdominal pain, vomiting and lethargy (specificity 92%) may indicate that an ultrasound is not needed prior to enema and that obtaining an ultrasound could delay definitive treatment potentially leading to complications. While this may be true, depending on ultrasound availability, the ultrasound could be obtained in lieu of the abdominal XRAY and if positive the patient would already be in the radiology suite.

TEST CHARACTERISTICS: CLINICAL AND IMAGING COMBINATIONS									
Ultrasound	X								
Abd XRAY*		X	X	X	X	X	X	X	X
Lethargy			X				X	X	X
Abd pain				X			X	X	X
Vomiting					X			X	X
Bloody stool						X			X
SENSITIVITY	97.2%	90.2%	28.3%	59.8%	73.9%	80.0%	16.3%	14.1%	10.0%
SPECIFICITY	93.1%	63.1%	87.8%	82.9%	68.3%	66.7%	92.7%	95.1%	93.3%
*Highly suggestive Abdominal XRAY: ≥ 1 of soft tissue mass, bowel obstruction, visible intussusception, sparse large bowel gas pattern									

APPLICABILITY: The validity concerns discussed may limit the generalizability of the study's result. The clinical findings of lethargy and abdominal pain may be somewhat subjective in an infant and toddler. Inter-rater reliability of these clinical findings, abdominal XRAY and ultrasound were not reported because of the retrospective study design.

AUTHOR'S CONCLUSION: "In conclusion, the combination of a highly suggestive abdominal radiograph, abdominal pain, and vomiting and lethargy was highly specific for intussusception, comparable to that of an ultrasound. This indicates that an ultrasound may not be needed before an enema for the diagnosis of intussusception in high-risk patients. In those without this combination, an ultrasound would be recommended as a less invasive test."

POTENTIAL IMPACT: The impact of this study on the diagnosis of intussusception when emergency ultrasound is not readily available is unclear. The validity concerns will limit its applicability until prospective data is available. Convincing our pediatric radiology colleagues to come in in the middle of the night without ultrasound confirmation of intussusception could be an insurmountable hurdle.

INTUSSUSCEPTION:
POINT OF CARE ULTRASOUND

In children with suspected intussusception what is the diagnostic accuracy of pediatric emergency physicians performed point of care ultrasound when compared to radiologist ultrasound in identifying those with and without ileocolic intussusception?

Alvira Shah, M.D., Karen Goodman, M.D.
May 2012

Riera A, Hsiao AL, Langhan ML, Goodman TR, Chen L.

DIAGNOSIS OF INTUSSUSCEPTION BY PHYSICIAN NOVICE SONOGRAPHERS IN THE EMERGENCY DEPARTMENT.

Ann Emerg Med. 2012 Sep;60(3):264-8.
PubMed ID: 22424652

STUDY DEFINITIONS	
POPULATION	Inclusion: Children with suspected ileocolic intussusception, ultrasonography in the diagnostic radiology department, eligible pediatric emergency physician sonographer available. Exclusion: None specified Setting: Single Children's Hospital ED. 7/2008-9/2011
DIAGNOSTIC TEST	Point of Care sonography performed pediatric emergency faculty (4) or fellow (2) A 1-hour focused training by a pediatric radiologist: Didactic component: Pathophysiology of intussusception, comprehensive series of still images: cases consistent with intussusception, normal bowel, or other intra-abdominal findings that are commonly construed as false positives. Hands-on scanning technique component: Child served as the pediatric model. Participants directly supervised by the pediatric radiologist. Scan technique: 1. Linear transducer in transverse orientation (indicator to the patients right) psoas identified at the appropriate depth in the RLQ, probe then swept up to RUQ. 2. Probe reoriented with indicator to patient's head and swept to the LUQ. 3. Probe reoriented in the transverse orientation and swept to the LLQ Positive ultrasound: "Target" or "bull's-eye" (represents intussuscepted bowel in cross-section
REFERENCE	Ultrasound performed by a pediatric radiologist
OUTCOME	Test characteristics
DESIGN	Observational: Prospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. The patients enrolled in the study were children with suspected ileocolic intussusception who were to undergo ultrasound evaluation for diagnostic confirmation.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The findings of the ultrasound done by PEM physicians were compared to interpretation of ultrasounds done subsequently by diagnostic radiologists.
Were those interpreting the test and reference standard blind to the other results?	Yes. The PEM physicians were blinded to the results of the radiologist's ultrasound findings but were not blinded to the patients' presenting characteristics. The radiologists interpreting the ultrasounds were not aware of the point of care ultrasound findings of the PEM physicians.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	Yes. All the children with suspected ileocolic intussusception were enrolled if they were to undergo ultrasound in the diagnostic radiology department and an eligible PEM physician sonographer was available.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

		RADIOLOGY ULTRASOUND		
		POSITIVE	NEGATIVE	
POINT OF CARE ULTRASOUND	POSITIVE	11	2	13
	NEGATIVE	2	67	69
		13	69	82

Location: RUQ = 62%, RLQ = 31%, LUQ = 7%

Prevalence: 13/82 = 16%
Sensitivity: 11/13 = 85%, 95% CI (54. 97%)
Specificity: 67/69 = 97%, 95% CI (89, 99%)
Predictive value (+) Test: 11/13 = 85% 95% CI (54, 97%)
Predictive value (-) Test: 67/69 = 97%, 95% CI (89, 99%)
Likelihood Ratio (+) Test: (11/13)/(2/69) = 29, 95% CI (7.3, 117)
Likelihood Ratio (-) Test: (2/13)/(67/69) = 0.16, 95% CI (0.04, 0.57)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Unclear. The study evaluated the efficacy of relatively novice ultrasonographers. The results would likely be reproducible though interrater reliability was not assessed
Are the study results applicable to the patients in my practice?	Yes. This study was done at an urban hospital with likely a similar patient population.
Will the test results change my management strategy?	Yes. A positive bedside ultrasound would help to initiate a radiology consult for confirmatory ultrasound or a diagnostic and therapeutic air contrast enema. A negative bedside ultrasound could not be used to “rule out” intussusception
Will patients be better off as a result of the test?	Yes. The prognosis may be improved if diagnosis can be made earlier and faster. This could potentially reduce complications of such as bowel ischemia/necrosis, decreased patient pain, and decreased need for operative intervention.

CLINICAL BOTTOM LINE

BACKGROUND: In the hands of experienced operators, ultrasonography is the criterion standard for the diagnosis of ileocolic intussusceptions. Since intussusception is a leading cause of bowel obstruction and ischemia in children, use of point of care ultrasound in the ED could lead to prompt recognition and initiation of therapy. Bedside ultrasound detection of intussusception would be especially advantageous in settings in which no comprehensive pediatric radiology services are available. A rapid diagnosis can facilitate expeditious transfer of patients to centers in which reduction can be performed. In institutions where pediatric radiology is available it enables a prompt diagnosis which can more efficiently prioritize the care of patients with suspected intussusception.

CLINICAL QUESTION: In children with suspected intussusception what is the diagnostic accuracy of pediatric emergency physicians performed point of care ultrasound when compared to radiologist ultrasound in identifying those with and without ileocolic intussusception?

DESIGN/RISK OF BIAS: This was a well-designed prospective cohort study that included 82 patients of which 16% had intussusception. The study could have benefited from a large sample of patients with intussusception (n=13). Point of care ultrasound was performed by relatively novice pediatric emergency faculty (4) or fellows (2) who received 1-hour focused training (1/2 hour didactic and ½ hour hands on practice) by a pediatric radiologist. 1 physician performed approximately 50% of the point of care ultrasounds.

PRIMARY RESULTS: The performance of bedside ultrasonography in this study exhibited high specificity with narrow confidence intervals (97%, 95% CI (89, 99%)), which would make it an excellent test to rule in intussusception. The lower sensitivity (85%, 95% CI (54, 97%)) makes point of care ultrasonography less useful as a screening test to rule out intussusception. The 2 false negative results include 1 patient found to have a self-reducing intussusception on the radiology exam and for 1 patient the bedside examiner did not use the appropriate probe and depth. Importantly, the technique used included imaging of all 4 quadrants as 38% of intussusceptions were found outside of the right upper quadrant.

APPLICABILITY: An assessment of interrater reliability would have improved the generalizability of the study's results. It is unclear if the training could be exported to other settings and in particular those settings without a pediatric radiologist available.

AUTHOR'S CONCLUSION: "With appropriate and focused training, pediatric emergency physicians can accurately diagnose ileocolic intussusception in children by using bedside ultrasonography."

POTENTIAL IMPACT: This prospective pilot study demonstrated good test characteristics of PEM physician–performed bedside ultrasonography for the diagnosis of intussusception in children after a single, focused training session. Further larger studies need to confirm the accurate use of bedside ultrasonography by trained PEM physicians before it can be routinely relied upon to both rule in and rule out ileocolic intussusception in children.

INTUSSUSCEPTION:
POINT OF CARE ULTRASOUND META-ANALYSIS

In pediatric patients with suspected intussusception, what is the diagnostic accuracy of emergency physician performed point of care ultrasound (POCUS) and radiology performed ultrasound (RADUS) and are the two comparable?

John Park, MD, Adriana Manikian, MD
July 2019

Tsou PY, Wang YH, Ma YK, Deanehan JK, Gillon J, Chou EH, Hsu TC, Huang YC, Lin J, Lee CC.

ACCURACY OF POINT-OF-CARE ULTRASOUND AND RADIOLOGY-PERFORMED ULTRASOUND FOR INTUSSUSCEPTION:
A SYSTEMATIC REVIEW AND META-ANALYSIS

Am J Emerg Med. 2019 Jun 4.
PubMed ID: 31182360

STUDY DEFINITIONS	
POPULATION	Inclusion: Patients: < 21 years, suspected intussusception Studies: Prospective and retrospective cohort studies Exclusion: Case reports, case series of < 10 patients, studies without original data Setting: U.S. (n=12), Europe (n=8), Asia (6), Other (n=4),
DIAGNOSTIC TESTS	Point-Of-Care UltraSound (POCUS): Training ≥ 1 hour didactic and ≥ 1 hour experience. Defined as Experienced, Unexperienced or Unknown Experience RAdiology Performed UltraSound (RADUS): Includes studies performed by ultrasound tech and interpreted by radiologist A positive ultrasound was defined as: Cross sectional view: Presence of Target or Donut sign Longitudinal view: Presence of Pseudo-kidney or Sandwich sign
REFERENCE STANDARD	≥ 1 of the following: 1. Barium or air enema 2. Ultrasound by experienced radiologist 3. Surgical findings 4. Clinical diagnosis Ultrasound Negative: Clinical judgement and/or Observation Ultrasound Positive: Enema and/or Surgical findings
OUTCOME	Test characteristics for POCUS and RADUS
DESIGN	Meta-analysis of prospective and retrospective cohort studies

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review include explicitly and appropriate eligibility criteria?	Unclear. The POCUS group included studies performed by both experienced and inexperience emergency physicians. Definitions of experience were study dependent. In addition, the didactic and experiential components of training were not specified. The article defines training as ≥ 1 hour of didactic and ≥ 1 hour of hands-on experience. A sensitivity analysis based on level of EM physician experience would have been helpful. For 2 studies the level of training of the EM physician was unknown. In addition, for 7 studies whether the ultrasound was performed by EM or radiology was unknown.
Was biased selection and reporting of studies unlikely?	Yes. The search included Medline and EMBASE from inception to 2/2018. Search terms were provided and there were no exclusions based on language or country. In addition, references of review articles and search identified articles were searched. Deek's test revealed a significant risk of publication bias. However, when two missing studies were imputed the summary log transformed diagnostic odds ratio did not change significantly (OR 6.31, 95% CI (5.48, 7.13) without the two additional studies → OR 6.05, 95% CI (5.2, 6.9) with the additional two studies.
Were the primary studies of high methodologic quality?	Unclear. QUADAS 2 was used to assess individual study quality (Figure 2). The authors described methodologic quality as "acceptable". There appears to be a significant risk of bias in the QUADAS categories of "flow and timing" and "reference standard".
Were assessment of studies reproducible?	No. Two reviewers assessed studies for inclusion. Differences were resolved by consensus or by a 3rd arbitrator. A kappa statistic was not presented for study inclusion or study quality.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

No. I^2 was 92% indicating significant heterogeneity among the study results. When outliers were excluded from the analysis the I^2 was 8%. The area under the receiver operating characteristic curve was similar with and without the outlier studies included. A random effects model was used to combine the data.

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 30 studies (n = 5,249 patient)
Publication: Manuscript (n=26), Conference abstract (n=4)
Setting: North America (n=13), Europe (n=7), Asia (n=6), Other (n=4)
Orientation to Time: Prospective (n=16), Retrospective (n=14)
Ultrasonographer: POCUS (n=7), RADUS (n=16), Unknown (n=7)
Patients: POCUS (n=1,491), RADUS (n=3,166), Unknown (n=593)
Location: ED (15), Inpatient (3), Unclear (12)
Reference Standard:
Clinical judgement AND Imaging (n=11)
Imaging alone (n=6)
Experienced radiologist (n=4)
Surgical confirmation (n=1)
Contrast enema OR Surgery (n=8)
Prevalence of Intussusception: 35.3% (range: 2% → 95%)

TEST CHARACTERISTICS

	SENSITIVITY	SPECIFICITY	LR (+) TEST	LR (-) TEST	AUROC
All (n=30)	98% (96, 98%)	98% (95, 99%)	43.8 (18, 106.7)	0.03 (0.02, 0.04)	0.99 (0.98, 1.0)
POCUS (n=7)	94% (88, 97%)	98 (62, 100%)	45 (1.7, 1,209)	0.06 (0.03, 0.13)	0.95 (0.94, 0.97)
RADUS (13)	98% (96, 99%)	97 (95, 99%)	35.9 (19.6, 65,6)	0.02 (0.01, 0.04)	1.00 (0.98, 1.0)

Meta-Regression: POCUS vs RADUS: No significant difference overall

Sensitivity Analyses:
1. RADUS studies with and without studies with an unclear ultrasonographer: No difference
2. Exclusion of single study with a population with cancer post-surgery: No difference

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. For the POCUS studies, the level of experience and training varied and in 2 studies the performer experience was not reported. In addition, the RADUS cohort included studies in which the ultrasound was performed by an ultrasound technician and interpreted by a radiologist. A kappa on ultrasound image acquisition and interpretation would have been helpful.
Are the study results applicable to the patients in my practice?	Yes. The inclusion of 30 studies of which 21 were conducted in North American or European centers likely makes the study's results generalizable to our pediatric patients with suspected intussusception. 35% of patients had intussusception though the range of 2-95% is very wide. The RADUS group had a prevalence of 42.4% while the POCUS group had a prevalence of 22.2%/
Will the results change my management strategy?	No. RADUS is our current diagnostic test for intussusception. The study's results could justify further training for POCUS performed by emergency physicians.
Will patients be better off as a result of the test?	Yes. A negative ultrasound can preclude the use of enema (invasive, radiation exposure) as a diagnostic test. Point of care ultrasound could potentially decrease ED length of stay for those with a negative study and decrease time to diagnosis and treatment in those with a positive study. Our radiology colleagues would need to accept a positive POCUS as an indication for contrast enema.

CLINICAL BOTTOM LINE

BACKGROUND: Abdominal XRAY was the original screening tool for intussusception but was neither sensitive nor specific. The most common XRAY reading in those with intussusception was “nonspecific bowel gas pattern”. Contrast enema (barium, air) was used to both confirm the diagnosis and perform the reduction. Ultrasound has become the study of choice to diagnose intussusception based on the test accuracy when it is performed by radiologists. The studies of point of care ultrasound performed by emergency physicians have demonstrated similar results but have been criticized for their small same size and unstandardized training regimens.

CLINICAL QUESTION: In pediatric patients with suspected intussusception, what is the diagnostic accuracy of emergency physician performed point of care ultrasound (POCUS) and radiology performed ultrasound (RADUS) and are the two comparable?

DESIGN/RISK OF BIAS: This was a meta-analysis of both prospective and retrospective cohort studies of the accuracy of ultrasound for the diagnosis of intussusception. It included patients less than 21 years of age with suspected intussusception.

Point of care ultrasound (POCUS) performed by emergency medicine physicians and radiology performed ultrasound (RADUS) were generally considered positive if a target or donut sign was seen on cross-sectional view or pseudo-kidney or sandwich sign were seen on longitudinal view.
The studies used a variety of reference standards. In general, those with a high suspicion of intussusception underwent confirmation by a contrast enema or surgical findings. Those with a low suspicion for intussusception were confirmed by clinical findings or observation. The primary outcome of the study were the test characteristics of ultrasound as a whole and in both the POCUS and RADUS cohorts individually.

The POCUS group included studies of emergencies physicians who were experienced inexperienced and of unclear experience. Definitions of experience were study dependent. In addition, the didactic and experiential components of training were not specified. The search for studies was extensive and without restrictions. Deek’s test revealed a significant risk of publication bias. When two missing studies were imputed, the summary log transformed diagnostic odds ratio did not change significantly.

QUADAS 2 was used to assess individual study quality (Figure 2). The authors described methodologic quality as “acceptable”. There appears to be a significant risk of bias in the QUADAS categories of “flow and timing” and “reference standard”.

Two reviewers assessed studies for inclusion and quality. Differences were resolved by consensus or by a 3rd arbitrator. A kappa statistic was not presented for study inclusion or quality.

PRIMARY RESULTS: 30 studies were included in the meta-analysis including 5,249 patients. The studies differed in type of publication (manuscript (26), conference abstract (4)), study country (North America (13), Europe (7), Asia (6), Other (4), orientation to time (prospective (16), Retrospective (14), ultrasonographer (Emergency Medicine MD (7), Radiologist (16), Unknown (7), location (ED (15), Inpatient (3), ? (12) and reference standard. The prevalence of intussusception ranged from 2% to 95% (35% overall).

Test characteristics for ultrasound were excellent. Meta-Regression revealed no statistically significant difference in the test characteristics for POCUS compared to RADUS. RADUS had a higher sensitivity, specificity and area under the receiver operating characteristic curve and a lower likelihood ratio of a negative test than POCUS though these differences was not statistically significant. There was also no difference in the test characteristics when unknown performer studies added to the RADUS cohort.

TEST CHARACTERISTICS					
	SENSITIVITY	SPECIFICITY	LR (+) TEST	LR (-) TEST	AUROC
All (n=30)	98% (96, 98%)	98% (95, 99%)	43.8 (18, 106.7)	0.03 (0.02, 0.04)	0.99 (0.98, 1.0)
POCUS (n=7)	94% (88, 97%)	98 (62, 100%)	45 (1.7, 1,209)	0.06 (0.03, 0.13)	0.95 (0.94, 0.97)
RADUS (13)	98% (96, 99%)	97 (95, 99%)	35.9 (19.6, 65,6)	0.02 (0.01, 0.04)	1.00 (0.98, 1.0)

Sensitivity analyses revealed no difference in the test characteristics of RADUS studies with and without studies with an unclear ultrasonographer and no difference with or without exclusion of single study with a population with post-surgery cancer patients. Additional sensitivity analyses based on abstract vs manuscript and based on EM physician level of experience would have been helpful.

APPLICABILITY: The inclusion of 30 studies of which 21 were conducted in North American or European centers likely makes the study's results generalizable to pediatric patients with suspected intussusception. 35% of patients had intussusception though the range of 2-95% is very wide However, the level of experience and training varied and in 7 studies who performed the ultrasound was unknown. In addition, the RADUS cohort included studies in which the ultrasound was performed by an ultrasound technician and interpreted by a radiologist. A kappa on ultrasound image acquisition and interpretation would have been helpful.

AUTHOR'S CONCLUSION: "To our knowledge, this is the first meta-analysis that summarizes the diagnostic accuracy of ultrasound for intussusception in children and compares the diagnostic accuracy between POCUS and RADUS. Our findings revealed that ultrasound has excellent sensitivity and specificity in detecting intussusception. Additionally, the meta-regression showed that the diagnostic accuracy of POCUS for intussusception is not significantly different from that of RADUS. Taken together, our findings not only validated the excellent diagnostic accuracy of ultrasound for diagnosing intussusception, but also supported the use of POCUS performed by clinicians at the bedside to diagnose intussusception."

POTENTIAL IMPACT: RADUS is our current diagnostic test for intussusception. A negative ultrasound can precludes the use of enema (invasive, radiation exposure) as a diagnostic test.

The study's results could justify further training in POCUS for emergency physicians. The use of POCUS could potentially decrease ED length of stay for those with a negative POCUS and decrease time to diagnosis and treatment in those with a positive POCUS. A subgroup analysis of inexperienced versus experienced EM providers would have been helpful and the extent of didactic and hands-on training to reach proficiency remains to be determined. Our radiology colleagues would need to accept a positive POCUS as an indication for a contrast enema.

APPENDIX: TEST CHARACTERISTIC RAW DATA CALCULATIONS

TEST CHARACTERISTICS[1]				
	ALL	POCUS	RADUS	UNKNOWN
Studies (n)	30	7	16	7
Patients (n)	5,250	1,491	3,166	593
Prevalence	35.3% (34.0, 36.6%	22.2% (20, 24%)	42.4% (40.7, 44.15)	30% (26.5, 33.8%)
Sensitivity	96.6% (95.7, 97,3%)	90% (86.3, 92,8%)	98% (97.1, 98.6%)	98.3% (95.2, 99.4%)
Specificity	97.7% (97.1, 98.1%)	98.4% (97.6, 99%)	97.4% (96.6, 98.1%)	96.6% (94.4, 98%)
PV (+)	95.8% (94.8, 96.6%)	94.3% (91.2, 96.4%)	96.5% (95.4, 87.4%)	92.6% (88, 95.5%)
PV (-)	98.1% (97.6, 98.5%)	97.2% (96.1, 98%)	98.5% (97.8, 99%)	99.3% (97.8, 99.7%)
LR (+)	42 (33.4, 51.7)	56.3 (36.6, 91.9)	37.7 (28.7, 50.4)	28.9 (17.4, 48.8)
LR (-)	0.04 (0.03, 0.044)	0.1 (0.07, 0.14)	0.02 (0.014, 0.04)	0.02 (0.01, 0.05)

1. Calculated from the raw data provided in Table 1 using the diagnostic test calculator at the Centre for Evidenced Based Medicine website: WEB LINK

TOXICOLOGY

1. Acetaminophen: N-Acetyl Cysteine Route: Ann EM. 2009

ACETAMINOPHEN:
N-ACETYL-CYSTEINE ROUTE

In patients with an Acetaminophen ingestion at high risk of hepatic toxicity as indicated by an Acetaminophen level at or above the nomogram treatment line, is a 20-hour Intravenous regimen of N-Acetylcysteine superior to a 72-hour Oral regimen of N-Acetylcysteine when administered 4-24 hours after the time of ingestion in reducing hepatic toxicity defined as an elevated serum aspartate amino transferase (AST) or alanine amino transferase (ALT) level?

Michael Mojica, M.D.
May 2017

Yarema MC, Johnson DW, Berlin RJ, Sivilotti ML, Nettel-Aguirre A, Brant RF, Spyker DA, Bailey B, Chalut D, Lee JS, Plint AC, Purssell RA, Rutledge T, Seviour CA, Stiell IG, Thompson M, Tyberg J, Dart RC, Rumack BH.

COMPARISON OF THE 20-HOUR INTRAVENOUS AND 72-HOUR ORAL ACETYLCYSTEINE PROTOCOLS FOR THE TREATMENT OF ACUTE ACETAMINOPHEN POISONING

Ann Emerg Med. 2009 Oct;54(4):606-14.
PubMed ID: 19556028

STUDY DEFINITIONS	
POPULATION	Inclusion: 20-hour Intravenous Cohort: • Acetaminophen poisoning identified by primary or secondary discharge diagnosis codes • Acute acetaminophen overdose: Ingestion over less than an 8-hour period • Acetaminophen level obtained 4-24 hours after ingestion and ≥ nomogram treatment line starting at 150 g/mL. • An aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level greater than 1,000 IU/L at any time, an AST or ALT level below 100 IU/L measured 36-72 hours after ingestion, or any AST or ALT value measured 72-96 hours post-ingestion. Inclusion: 72-hour Oral Cohort • Acetaminophen level between 4 and 24 hours after their ingestion ≥ the nomogram treatment line starting at 150 g/mL OR an estimated ingestion of > 7.5 g (adult) or 140 mg/kg (child). • Serum aminotransferase levels, electrolyte levels, and coagulation profile followed at least once daily Exclusion: None specified Setting: 72-hour Oral Cohort: American database (hospitals in all 50 states), 1975-1985. 20-hour Intravenous Cohort: Canadian database (n=34 hospitals), 1980-2005. Both cohorts included community and academic centers, pediatric and adult centers and transplant centers.
INTERVENTION	72-hour Oral regimen of Acetylcysteine initiated 4-24 hours after ingestion with 140 mg/kg orally followed by 70 mg/kg every 4 hours for 17 doses
CONTROL	20-hour Intravenous regimen of Acetylcysteine initiated 4-24 hours after ingestion with 150 mg/kg infusion over 15 to 60 minutes, 50 mg/kg over 4 hours, and 100 mg/kg over 16 hours.
OUTCOME	Primary Outcome: Hepatotoxicity: Peak serum aspartate amino transferase (AST) or alanine amino transferase (ALT) level greater than 1,000 IU/L Sensitivity Analysis: Effect of removing acute or chronic ethanol use Secondary Outcomes 1. Death: Due to acetaminophen-induced hepatic failure versus other causes. 2. Referral for liver transplant 3. Anaphylactoid reactions: Episode of pruritus, urticaria, facial flushing, edema, stridor, shortness of breath, wheezing, cough, or low blood pressure associated with the acetylcysteine
DESIGN	Observational: Retrospective cohort (two populations, one an historical cohort)

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
ASIDE FROM THE EXPOSURE OF INTEREST DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or did statistical adjustments address the imbalance).	No. There were statistically significant differences between the groups for age, time to treatment with acetylcysteine, extrapolated 4-hour acetaminophen level, and acute and chronic ethanol use. Regression analysis was used to determine the independent effect of treatment regimen while controlling for several potential confounders including the factors that were significantly different between treatment regimens.
Were the circumstances and methods for detecting the outcome similar?	Yes. Medical record review was standardized. Patients were first identified by discharge ICD9 codes. 75 variables were then abstracted from the medical records all with a high degree of inter-rater reliability (kappa ≥ 0.8). The primary outcome was an objective laboratory finding.
Was follow-up sufficiently complete?	Unclear. Figure 1 indicates the patient selection process. The breakdown of indications for exclusion was not available for the 72-hour cohort. For the 20-hour cohort a high proportion of patients were excluded for reasons not specific in the inclusion/ exclusion criteria indicating the possibility of selection bias.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

20-hour IV cohort: n = 2,086
72-hour PO cohort: n = 1,962

RISK OF HEPATOTOXICITY (UNADJUSTED)

	HEPATOTOXICITY		
	YES	NO	
20-HOUR IV REGIMEN	289	1,797	2,086
17-HOUR PO REGIMEN	310	1,652	1,962

20-hour Regimen: 289/2,086 = 13.9%
72-hour Regimen: 310/1,962 = 15.8%
Risk Difference: 13.9 - 15.8 = -1.9%, 95% CI (-4.2, 0.3%)
Relative Risk = 13.9/15.8 = 0.88, 95% CI (0.76, 1.02)

The sample size determination indicates that the authors considered a 3.3% difference in the rate of hepatic toxicity to be clinically significant.

RELATIVE RISK OF HEPATOTOXICITY*

TIME TO TREATMENT	RELATIVE RISK (95% CI)
4 hours	0.54 (0.38, 0.75)
12.2 hours	0.84 (0.71, 1.0)
18.5 hours	1.19 (1.0, 1.4)
24 hours	1.61 (1.22, 2.12)
*Adjusted Relative Risk (20 Hour/72 Hour)	

<u>Deaths Attributable to Acetaminophen Toxicity</u>
Risk 20-hour regimen = 1/2,086 = 0.05%
Risk 72-hour regimen = 3/1962 = 0.15%
Risk Difference: -0.1% (-0.4, 0.1%)
All deaths treated ≥ 19.5 hours after ingestion

<u>Anaphylactoid Reactions</u>
20 hours IV: 148/2,086 = 7.1%, 95% CI (6.1, 18.3%)
77% (114/148) were limited to cutaneous reactions

HOW PRECISE IS THE ESTIMATE OF THE RISK?

See the confidence intervals for the risk differences and relative risks above. The large sample size resulted in relatively narrow confidence intervals. The confidence intervals for the risk difference for hepatotoxicity includes 0 indicating that the difference is not statistically significant. The risk difference is also less than the 3.3% that the authors selected as a clinically significant difference.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Yes. The study included multiple centers across the US and Canada. Both cohorts included community and academic centers, pediatric and adult centers and transplant centers. Generalizability to those with co-morbidities (particularly hepatic disease) and those with co-ingestants other than alcohol is not clear.
Was follow-up sufficiently long?	Likely yes. Patient's data was available until hospital discharge. The time of the last liver function tests since the time of ingestion was not reported. It seems reasonable to assume that patients did not get discharged until after the establishing a downward trend in their transaminases though this was not reported.
Is the exposure similar to what might occur in my patient?	Yes. Acetaminophen is readily available and a common ingestion. The study did not indicate if co-ingestants were involved.
Are there any benefits that offset the risks associated with exposure?	The 20-hour intravenous regimen was associated with a lower risk of hepatotoxicity when administered in the first 8 hours after ingestion of Acetaminophen. However, 7.1% of patients in the 20-hour regimen had an anaphylactoid reactions. The number needed to harm (NNH = 1 /0.071) is 14. For every 14 patients treated with the 20-hour intravenous regimen 1 patient will develop an anaphylactoid reaction. 77% of the reaction were limited to cutaneous manifestations.

CLINICAL BOTTOM LINE

BACKGROUND: Acetaminophen toxicity is a leading cause of toxicologic morbidity and mortality. Approximately half of the cases of liver failure in the U.S. are attributable to Acetaminophen. N-acetylcysteine can prevent or halt the progression of liver toxicity if administered early. However, the optimal dose and route of administration are not known. The U.S., has traditionally used a 72-hour oral regimen while much of the world uses a 20-hour intravenous regimen. There have been no studies that have directly compared the two regimens though there is data to suggest that the two regimens may be equivalent when initiated within 8-10 hours of ingestion and the 72-hour regimen may be better after 8-10 hours.

CLINICAL QUESTION: In patients with an Acetaminophen ingestion at high risk of hepatic toxicity as indicated by an Acetaminophen level at or above the nomogram treatment line is a 20-hour intravenous regimen of N-acetylcysteine superior to a 72-hour oral regimen of N-acetylcysteine when administered 4-24 hours after the time of ingestion in reducing hepatic toxicity as defined by an elevated serum aspartate amino transferase (AST) or alanine amino transferase (ALT) level?

DESIGN/RISK OF BIAS: This is a usual study design in that it used two separate cohorts of patients enrolled in different countries over different time periods. The later Canadian cohort received a 20-hour regimen of intravenous acetylcysteine and the earlier US cohort received at 72-hour regimen of oral acetylcysteine. The primary analysis included 2,086 patients in the 20-hour intravenous cohort and 1,962 patients in the 72-hour oral cohort. In the 20-hour cohort 75 variables with a high degree inter-rater reliability (kappa ≥ 0.8) were included. Data abstractors were blinded to the study hypothesis.

The study is susceptible to biases inherent to retrospective observational studies. Inclusion and exclusion criteria were similar though not identical and the possibility in an improvement in supportive care for the later cohort cannot be excluded. The presence of co-ingestants was not reported. Elevated transaminases are a laboratory marker of liver damage but not a patient oriented outcome.

Finally, the study assessed composite interventions that included differences in the route, total dose, duration and rate of administration. it is not impossible to determine the independent impact of each of those factors.

PRIMARY RESULTS: There was no statistically significant difference in the rate of hepatotoxicity between the 20-hour intravenous regimen and the 72-hour oral regimen in the unadjusted analysis. (Risk Difference: 13.9% – 15.8% = -1.9%, 95% CI (-4.2, 0.3%), Relative Risk = 0.88, 95% CI (0.76, 1.02)). However, the relative risk of toxicity was dependent on the time to initiation of therapy. When N-acetylcysteine was administered within 12 hour of Acetaminophen ingestion there was a decreased risk of hepatotoxicity in the 20-hour regimen compared to the 72-hour regimen. There was no difference in the rate of hepatotoxicity for the two regimens when N-acetylcysteine was administered between 12 and 18 hours after Acetaminophen ingestion. When N-acetylcysteine was administered more than 18 hours after Acetaminophen ingestion there was a decrease risk of hepatotoxicity in the 72-hour regimen compared to the 20-hour regimen.

Anaphylactoid reactions occurred in 7.1%, 95% CI (6.1, 18.3%) of the patients receiving the 20-hour intravenous regimen. 77% (114/148) were limited to cutaneous reactions. The number needed to harm is 14. For every 14 patients treated with the 20-hour intravenous regimen 1 patient will develop an anaphylactoid reaction. 51% of those with reaction had their infusion stopped either completely of transiently.

RELATIVE RISK OF HEPATOTOXICITY*	
TIME TO TREATMENT	RELATIVE RISK (95% CI)
4 hours	0.54 (0.38, 0.75)
12.2 hours	0.84 (0.71, 1.0)
18.5 hours	1.19 (1.0, 1.4)
24 hours	1.61 (1.22, 2.12)
*Adjusted Relative Risk (20 Hour/72 Hour)	

APPLICABILITY: The study's results are generalizable to a wide variety of patients and settings. The study included multiple centers across the US and Canada. In addition, both cohorts included community and academic centers, pediatric and adult centers and transplant centers. Generalizability to those with co-morbidities (particularly hepatic disease) and those with co-ingestants other than alcohol is not clear.

AUTHOR'S CONCLUSION: "In conclusion, the comparison of Canadian patients who began receiving the 20-hour intravenous acetylcysteine protocol with the historical cohort of US patients treated with the 72-hour oral protocol suggests that for individuals presenting early after an acute acetaminophen overdose, the risk of hepatotoxicity was lower when the 20-hour intravenous acetylcysteine protocol was initiated. With increasing delay to treatment, the risk of hepatotoxicity was lower when the 72-hour oral protocol was administered. No difference was observed between the groups with respect to death or liver transplant."

POTENTIAL IMPACT: The study's results indicate that the choice of N-acetylcysteine regimen is dependent on the time since ingestion. The rate of anaphylactoid reactions with the 20-hour intravenous regimen may be justified in the first 8 hours after ingestion of Acetaminophen when the 20-hour intravenous regimen demonstrated a decreased risk of hepatotoxicity compared to the 72-hour oral regimen. The risk of anaphylactoid reactions may not be acceptable when N-acetylcysteine is administered between 8 and 12 hours of ingestion when there is no difference between the 2 regimens and when N-acetylcysteine is administered after 12 hours since ingestion when there is a lower rate of hepatotoxicity with the 72-hour oral regimen. A large, randomized, controlled trial comparing the two regimens would improve upon the risks of bias inherent to retrospective observational studies.

Subsequent to this study the duration of the initial dose of intravenous acetylcysteine increased to 1 hour to decrease the rate of anaphylactoid reactions. In addition, the intravenous regimen are often continued beyond 20 hours (as it was in 20% of the patients in the intravenous group in this study) in patients with significant hepatotoxicity or persistently high acetaminophen levels.

TRAUMA

1. Abdominal: PO Contrast (PECARN): Ann Emerg Med. 2015
2. Abdominal: Decision Rule Derivation (PECARN): Ann EM. 2013
3. Abdominal: Pain and Physical Exam Accuracy: J Peds 2014
4. C-SPINE: Adult Nexus Criteria Validation: N Engl J Med. 2000
5. C-SPINE: Consensus Based Algorithm: J Pediatr Surg. 2017
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7. C-SPINE: Re-DerivationRule (PECARN): Pediatrics: 2019
8. C-SPINE: Pediatric NEXUS Criteria Validation: Pediatrics. 2001
9. C-SPINE: Toddler Decision Rule Derivation: J Trauma. 2009
10. Concussion: Return To Physical Activity Timing: JAMA 2016
11. FAST Exam: Pediatric Accuracy: J Tr Acut Car Surg. 2017
12. FAST Exam: Utility in Pediatric Torso Trauma: JAMA 2017
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14. Head: Decision Rule Derivation (PECARN): Lancet. 2009
15. Head: Decision Rule Impact Analysis (PECARN): Peds. 2017
16. Head: Hyperosmolar Therapy for TBI: Crit Care Med: 2019

17. Head: ICU Admission Decision Rule: PEC. 2016
18. Head: ICU AdmiT Decision Rule (PECARN): JAMA Peds 2017
19. Head: Isolated Scalp Hematoma (PECARN): Annals EM. 2014
20. Head: Machine Learning vs PECARN: JAMA Peds: 2019
21. Head: Late Presenting TBI (PREDICT): Annals EM: 2019
22. Head: Point of Care US for Skull Fractures: J Peds 2018
23. Head: Quick Brain MRI: J Neurosurg Pediatr. 2016
24. Hemorrhagic Shock: Hypotensive Resus: J Trauma 2002
25. Hemorrhagic Shock: Ped TXA Safety: Ped Crit Care Med 2018
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28. Lacerations: Pediatric Absorbable Sutures: Acad EM 2004
29. Primary Surv: Whole Body vs Selective CT: JAMA Peds 2018

ABDOMINAL TRAUMA:
CT ORAL CONTRAST UTILITY

In patients 0-18 years old with blunt torso trauma how accurate is abdominal CT with intravenous and oral contrast when compared to abdominal CT with intravenous contrast only in identifying those with and without an intra-abdominal injury?

Sheri-Ann Wynter, M.D., Joanne Agnant, M.D.
August 2015

Ellison AM, Quayle KS, Bonsu B, Garcia M, Blumberg S, Rogers A, Wootton-Gorges SL, Kerrey BT, Cook LJ, Cooper A, Kuppermann N, Holmes JF;
Pediatric Emergency Care Applied Research Network (PECARN)

USE OF ORAL CONTRAST FOR ABDOMINAL COMPUTED TOMOGRAPHY IN CHILDREN WITH BLUNT TORSO TRAUMA.

Ann Emerg Med. 2015 Aug;66(2):107-114.
PubMed ID: 25794610

STUDY DEFINITIONS	
POPULATION	Inclusion: 0-18 years old with blunt torso trauma; evaluated at a PECARN ED, undergoing abdominal CT with IV contrast Exclusion 1. Preexisting neurological disorders 2. Injury occurred > 24 hours prior to presentation 3. Transfers with a prior abdominal CT or DPL 4. Unknown if oral contrast was administered Setting: 20 Children's Hospital (PECARN network). 5/2007-1/2010
TESTS	Abdominal CT with IV contrast only Abdominal CT with IV and oral contrast (Oral contrast use based on the participating centers' guidelines and discretions)
REFERENCE STANDARD	Intra-abdominal injury: Injury involving the spleen, liver, pancreas, urinary tract, adrenal glands, or gastrointestinal tract, identified during the patient's ED stay or hospitalization. Gastrointestinal injuries: Injury to the hollow viscous or associated mesentery from the stomach to the rectum. Solid organ injuries: Liver, kidneys, or spleen. Definitive abdominal testing: Abdominal CT scan, laparotomy or laparoscopy, or autopsy performed.
DEFINITIONS	CT Positive: Intra-abdominal injury identified: Injury to spleen, liver, pancreas, urinary tract, adrenal glands or gastrointestinal tract CT Abnormal: Met criteria for a Positive CT OR findings *suggestive* of intra-abdominal injury: intraperitoneal fluid/air, extravasation of contrast or intestinal wall edema not associated with an intra-abdominal injury (IAI) High-risk mechanism of injury: motor vehicle collision with ejection, rollover, or death in the same collision; motor vehicle collisions > 20 miles per hour and the patient unrestrained, falls greater than 10 feet; pedestrians or bicyclists struck by vehicles moving greater than 20 miles per hour; or bicycle collision with handlebars striking the abdomen. Abdominal pain: > 2 years, complaint of pain in or over the abdomen. Abdominal tenderness: Any age, stated that palpation caused pain or grimaced on palpation of the abdomen. Seat belt sign: A continuous area of erythema, ecchymosis, or abrasion across the abdomen due to a seat belt restraint.
OUTCOME	Test characteristics
DESIGN	Observational: Prospective cohort

ARE THE RESULTS VALID?	
Did participating patients present a diagnostic dilemma?	Yes. Patients were those with blunt torso injury, but the presence of intra-abdominal injury was unknown.
Did investigators compare the test to an appropriate, independent reference standard?	No. Abdominal CT with IV and oral contrast (the test) was compared to either Abdominal CT with IV contrast, laparotomy or laparoscopy, or autopsy. Abdominal CT with IV contrast was used as the reference standard because this is the current accepted management for appropriate work-up to evaluate intra-abdominal organs after trauma. However, autopsy and laparotomy or laparoscopy cannot be ethically done on everyone. The test served as its own reference standard if an autopsy, laparotomy or laparoscopy were not done.
Were those interpreting the test and reference standard blind to the other results?	No. Those interpreting the test (radiologists) were blinded to the other results, as both test and reference standard were not done to both.
Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	No. See Table 3. Test or reference standard was performed at the discretion of the emergency physician. Table 3 shows those patients who were missed by initial CT and underwent laparoscopy/laparotomy or autopsy for definitive diagnosis. In these cases, these were used as the reference standard.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

		INTRA-ABDOMINAL INJURY (IAI)		
		YES	NO	
ABDOMINAL CT IV ONLY CONTRAST	ABNORMAL	546	658	1,204
	NORMAL	13	2760	2,773
		559	3,418	3,977

CHARACTERISTIC	CALCULATION	NUMBER (95% CI)
Prevalence IAI	555/3,977	14%
Sensitivity	546/559	97.7% (96.1, 98.6%)
Specificity	2,760/3,418	80.8% (79.4, 82%)
Predictive Value (+) Test	546/1,204	45.4% (42.6, 48.2%)
Predictive Value (-) Test	2,760/2,773	99.5% (99.2, 99.7%)
Likelihood Ratio (+) Test	(546/559)/(658/3,418)	5.1 (4.7, 5.4)
Likelihood Ratio (-) Test	(13/559)/(2,760/3,418)	0.03 (0.02, 0.05)

		INTRA-ABDOMINAL INJURY (IAI)		
		YES	No	
ABDOMINAL CT IV + PO CONTRAST	ABNORMAL	126	135	261
	NORMAL	1	748	749
		127	883	1,010

CHARACTERISTIC	CALCULATION	NUMBER (95% CI)
Prevalence IAI	127/1,010	12.5%
Sensitivity	126/127	99.2% (95.7, 99.9%)
Specificity	748/883	84.7% (82.2, 86.9%)
Predictive Value (+) Test	126/261	48.3% (42.3, 54.3%)
Predictive Value (-) Test	748/749	99.9% (99.2, 100%)
Likelihood Ratio (+) Test	(126/127)/(135/883)	6.5 (5.6, 7.6)
Likelihood Ratio (-) Test	(1/127)/(748/883)	0.009 (0.001, 0.065

Confidence intervals calculated at the Centre for Evidence Based Medicine website (LINK)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	There is no determination of inter-observer reliability because only the staff radiologist at specific institutions interpreted the CT scans.
Are the study results applicable to the patients in my practice?	Yes. We see children with blunt torso trauma (and enrolled patients in this study) and have the capabilities to obtain CT scans of the abdomen with IV contrast and with and without oral contrast. Prevalence of intra-abdominal injury in the population was 14% (686/4,987).
Will the results change my management strategy?	Results suggest that the addition of oral contrast may slightly increases the specificity, and therefore may improve the chances of ruling in intra-abdominal injury. However, this should be balanced by the risks associated with oral contrast. Oral contrast may cause emesis, prolonged length of time prior to imaging, and may obscure solid organ injury.
Will patients be better off as a result of the test?	No. Less use of oral contrast can decrease the time to CT scan and decrease the likelihood of missed solid organ injuries secondary to opacified bowel.

CLINICAL BOTTOM LINE

BACKGROUND: Children with blunt torso trauma present an interesting clinical diagnostic challenge. They are at risk for solid organ as well as gastrointestinal injuries. Abdominal CT scans with IV contrast are typically used to evaluate these children. However, some institutions routinely use oral contrast as well. Prior studies, including one randomized clinical trial, have characterized the test characteristics of these modalities but have been limited by small sample sizes. This study is a sub-analysis of a larger prospective PECARN study on blunt torso trauma in children, and is the largest study to compare the test characteristics of Abdominal CT with intravenous contrast versus Abdominal CT with intravenous and oral contrast.

CLINICAL QUESTIONS: In patients 0-18 years old with blunt torso trauma how accurate is abdominal CT with intravenous and oral contrast when compared to abdominal CT with intravenous contrast only in identifying those with and without an intra-abdominal injury?

DESIGN/VALIDITY: This is an observational study of two diagnostic tests. The study included 3,977 patients with a CT with only intravenous contrast and 1.010 patients with an abdominal CT with both intravenous and oral contrast. The study defined intra-abdominal injuries as injury involving the gastrointestinal tract (stomach to rectum), spleen, liver, pancreas, urinary tract, or adrenals.

This was a well-designed study but with significant limitations that are acknowledged by the authors

1. Indications for CT and oral contrast are not known
2. The reference standard was Abdominal CT, laparoscopy/laparotomy, or autopsy. However, few children had surgery or additional investigation. Essentially the test acted as its own reference standard in most cases. This can inflate the test characteristics.
3. The mean time to CT scan was 90 minutes but the CT scans were not reviewed to determine how far the contrast had traveled. A conclusion that CT without PO contrast performs similarly to with PO contrast must consider that the time for PO contrast to reach the desired level of the gastrointestinal tract may have been inadequate.
4. Follow-up was completed for 76% of the study sample.

PRIMARY RESULTS: There is a slightly higher specificity of intra-abdominal injury with the use of oral contrast, but similar sensitivities. However, likelihood ratios indicate that both Abdominal CT with intravenous contrast and Abdominal CT intravenous and oral contrast are better tests if they are negative with IV+PO contrast is much better than IV only if negative. The authors conclude that the test characteristics of Abdominal CT with IV contrast only and IV+PO contrast are so similar, that the use of oral contrast may be unnecessary when the delay to obtain such a scan is considered.

TEST CHARACTERISTIC COMPARISON		
	ABDOMINAL CT WITH CONTRAST	
	INTRAVENOUS	INTRAVENOUS + ORAL
Prevalence	14%	12.5%
Sensitivity	97.7% (96.1-98.8)	99.2 (99.5-100)
Specificity	80.8% (79.4-82.1)	84.7 (82.2-87.0)
Predictive Value (+) Test	45.4%	48.3
Predictive Value (-) Test	99.5%	98.6
Likelihood Ratio (+) Test	5.1	6.5
Likelihood Ratio (-) Test	0.029	0.009

APPLICABILITY: The study is largely generalizable to ED populations with a similar prevalence. The prevalence of intra-abdominal injury in this study was 14%. Although there are some key limitations to this study, including the validity concerns addressed above, and the observational design, the large sample size studied is beneficial.

AUTHOR'S CONCLUSIONS: "Oral contrast is used in a substantial proportion of children undergoing abdominal CT scanning after blunt torso trauma, and its use is highly variable across pediatric hospitals. Similar test characteristics exist between abdominal CT scans performed with and without oral contrast for these patients, suggesting that routine use may be unnecessary and delays obtaining CT scans for children at risk for intra-abdominal injuries."

POTENTIAL IMPACT: The similar test characteristics and prolonged time to imaging supports the use of intravenous contrast only to evaluate for intra-abdominal injuries after blunt torso trauma. Oral contrast may be administered if time permits in those patients with a high suspicion of pancreatic or gastrointestinal tract injury based on clinical or laboratory data.

ABDOMINAL TRAUMA:
DECISION RULE DERIVATION (PECARN)

In children with blunt torso trauma (chest, abdomen) presenting to the Pediatric Emergency Department who are evaluated by abdominal CT or clinical follow-up, do history and physical exam factors adequately identify those with and without intra-abdominal injury requiring acute intervention (IAI-Intervention)?

Rebecca Burton, M.D., Lilia Reyes, M.D.
March 2013

Holmes JF, Lillis K, Monroe D, Borgialli D, Kerrey BT, Mahajan P, Adelgais K, Ellison AM, Yen K, Atabaki S, Menaker J, Bonsu B, Quayle KS, Garcia M, Rogers A, Blumberg S, Lee L, Tunik M, Kooistra J, Kwok M, Cook LJ, Dean JM, Sokolove PE, Wisner DH, Ehrlich P, Cooper A, Dayan PS, Wootton-Gorges S, Kuppermann N.
Pediatric Emergency Care Applied Research Network (PECARN).

IDENTIFYING CHILDREN AT VERY LOW RISK OF CLINICALLY IMPORTANT BLUNT ABDOMINAL INJURIES.

Ann Emerg Med. 2013 Aug;62(2):107-116.
PubMed ID: 23375510

STUDY DEFINITIONS	
POPULATION	Inclusion: GCS <15 with blunt torso trauma Blunt trauma with: paralysis, multiple nonadjacent long bone fractures, Blunt torso trauma due to: MVC ≥ 45 mph with rollover, ejection. Automobile ≥ 5 mph versus pedestrian, bicyclist, fall > 20 feet, crush injury to the torso, physical assault involving the abdomen Physician concern for abdominal trauma resulting in Abdominal CT, ultrasound (FAST), laboratory testing, chest or pelvic radiography Exclusion: Injury > 24 hours' prior, penetrating trauma, preexisting neurologic disorders impeding reliable examination, known pregnancy, previous abdominal CT or diagnostic peritoneal lavage at another hospital Setting: 20 Children's hospitals EDs (PECARN Network). 5/2007-1/2010
RULE PARAMETERS	Standardized data collection form of history and physical examination findings
REFERENCE STANDARD	Intra-abdominal injury (IAI): Radiographically or surgically injury to spleen, liver, urinary tract (from the kidney to the urinary bladder), gastrointestinal tract (including the bowel or associated mesentery from the stomach to the sigmoid colon), pancreas, gallbladder, adrenal gland, intra-abdominal vascular structure, or traumatic fascial defect (traumatic abdominal wall hernia) Acute intervention: IAI associated with: Death caused by the intra-abdominal injury, a therapeutic intervention at laparotomy, angiographic embolization to treat bleeding from the intra-abdominal injury, blood transfusion for anemia due to hemorrhage from the intra-abdominal injury, or administration of intravenous fluids for 2 or more nights in patients with pancreatic or gastrointestinal injuries. CT scan of abdomen/pelvic at MD discretion Clinical follow-up of patients without imaging: Review of inpatient medical records Phone follow-up ≥ 7 days or mailed questionnaire or medical/local morgue records
OUTCOME	Rule characteristics Reduction in resource utilization
DESIGN	Observational: Prospective cohort

ARE THE RESULTS VALID?	
Were all important predictors included in the derivation process?	Yes (See Figure 2). The list of predictors included in the derivation process was extensive and well considered. The predictors were selected based on the existing medical literature and biologic or physiologic plausibility. Predictors were excluded from inclusion in the final clinical decision rule if they were not documented on > 5% of the data entry forms (implying that assessment of that predictor was not feasible in the general ED setting), and all predictors included in the final rule had good inter-rater reliability (Kappa > 0.6).
Were all important predictors present in significant proportion of the study population?	Unclear, but likely yes. The least common predictor prevalence in the final clinical decision rule was presence of diminished or absent breath sounds, which was found in 25/200 (13%) of children with intra-abdominal injury undergoing acute intervention. See Table E3. Significant associations on bivariable analysis of variables for intra-abdominal injury undergoing acute intervention, for data on prevalence of each of the clinical predictors in the study population.
Were the outcome event and predictors clearly defined?	Yes. The outcome events; Intra-Abdominal Injury (IAI) and Intra-Abdominal Injury undergoing acute intervention (IAI-Intervention) are clearly defined. The clinical predictors are clearly defined in Figure 2.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	It is unclear whether those assessing the outcome event (IAI and/or IAI-Intervention) were blinded to the presence of the predictors. The radiologists reading the abdominal CT to assess for IAI may have been blinded, depending on how much information was documented on the CT request form. It is highly unlikely that the pediatric surgeons, interventional radiologists, and other care providers performing “acute interventions” for IAI such as therapeutic laparotomy, angiographic embolization, and administration of PRBCs or IVF were blinded to presence of predictors. In is unlikely if knowledge of the predictors would affect the objective outcomes. However, knowledge of the predictors may have resulted in a choice of reference standard (e.g. laparotomy). Physicians responsible for documenting presence or absence of predictors on a standardized data entry form were temporally blinded to the outcome event, as they were to fill out the data entry forms prior to obtaining abdominal CT or other outcome results.
Was the sample size adequate (including an adequate number of outcome events)?	Yes. In general, for logistic regression it is recommended that 10 outcomes should be for every predictor in the rule. 7 predictors were identified so 70 outcomes would be required. Patients with IAI: N = 761 (6.3%) Patients with IAI-Intervention: N = 203 (1.7%)

WHAT ARE THE RESULTS?	
How well did the rule correctly predict patients with the primary outcome? How precise was this measurement?	Total sample size: N = 12,044 Sensitivity: 97%, 95% CI (93.7. 98.9%) Predictive Value of a Positive Rule: 2.8%, 95% CI (2.4, 3.2%)
How well did the rule correctly predict patients without the primary outcome? How precise was this measurement?	Specificity: 42.5%, 95% CI (41.6, 43.4%) Predictive Value of a Negative Rule: 99.9%, 95% CI (99.7, 100%)
How would use of the rule impact resource utilization?	If the rule were utilized as a directive rule, patients with negative rule could not have a CT (41.8% (5,034/12,044)) and patients with a positive rule would have a CT (58.2% (7,010/12,044)). The impact of the rule on resource utilization will depend on the baseline rate of CT utilization before rule application. 45.8% (5,514/12,044) of the patients in the study had an abdominal CT. If the rule was applied as a directive rule, the CT rate would increase by 12.4% to 58.2%. The authors state that it is not their intent that a patient with any of the predictors necessarily require a CT scan.
Was there an internal statistical validation of the results? How did it compare to the primary results?	No. An internal statistical validation of the results was not performed.
At what level of development is this rule? (see appendix)	☐ I ☐ II ☐ III ■ IV This a stage IV decision rule. The rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. Stage IV rules require further validation before it can be applied clinically.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Does the rule make clinical sense?	Yes. The rule makes clinical sense. It is relatively simple, has a reasonable number of criteria (7), the predictors are objective and reproducible and predictors are based on existing clinical practice. The rule would perhaps make more clinical sense if other commonly utilized clinical tools such as results of the bedside FAST (Focused Assessment Sonography for Trauma) exam and/or basic screening labs (i.e. UA for hematuria, transaminases, etc.) were included as predictors. Inclusion of these tools as predictors would likely have improved the rules sensitivity. The 6 patients missed by the clinical decision rule all had abnormalities that would likely have been identified by FAST and/or basic screening labs.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Yes. The authors of the study were careful to only include predictors in the final rule that had decent inter-rater reliability. All predictors in the clinical decision rule had kappa values of > 0.6, with the lower bound of the confidence intervals > 0.4.
Is the rule applicable to the patients in my practice?	Yes, the patients in our practice are like the patients in the study. Bellevue was one of the sites included in the study. Applicability to other clinical settings is unclear, though the study's large sample size should theoretically make the rule generalizable.
What are the benefits of applying the rule to my patients?	Identification of patients at very low risk for intra-abdominal injury undergoing acute intervention (risk 0.1% for patients with a negative rule) would potentially benefit them by allowing them to avoid the risks associated with undergoing abdominal CT scan, including significant radiation exposure with its consequent risks of future malignancy and sedation risk for many patients.
What are the risks of applying the rule to my patients?	The risks of applying this clinical decision rule, are missing or delaying diagnosis of patients with intraabdominal injury requiring intervention. Strict application of the rule, with abdominal CT scans ordered for any patient with a positive rule, has the potential to increase CT scanning rate in some settings.

CLINICAL BOTTOM LINE

BACKGROUND: Intra-abdominal injury is a relatively infrequent but significant cause of morbidity in children following trauma. Early identification of intra-abdominal injury that requires acute intervention (IAI-Intervention), such as therapeutic laparotomy, angiographic embolization, or requirement for blood transfusion or intravenous fluid resuscitation, is essential to decrease morbidity and mortality. Abdominal/pelvic CT scans have become an important tool in the evaluation of children for IAI-Intervention, but their use is associated with radiation exposure and consequent risk for future malignancy. Development of a means to correctly identify children at very low risk for IAI-Intervention would potentially protect many children from unnecessary scanning.

Several retrospective, small, single-center studies have suggested that children with blunt torso trauma may be risk stratified for IAI-Intervention based on clinical variables. The PECARN network of 20 Pediatric Emergency Department sites across the United States collaborated to derive a clinical decision rule to identify children at very low risk (0.1%) for IAI-Intervention.

CLINICAL QUESTION: In children with blunt torso trauma (chest, abdomen) presenting to the Pediatric Emergency Department who are evaluated by abdominal CT or clinical follow-up, do history and physical exam factors adequately identify those with and without intra-abdominal injury requiring acute intervention (IAI-Intervention)?

DESIGN/VALIDITY: This study was well designed without major methodologic flaws. The study enrolled 12,044 patients of which 761 (6.3%) had an intra-abdominal injury and 203 (1.7%) had an intra-abdominal injury requiring intervention. Predictors and outcomes utilized in the rule are well-defined, and all predictors have decent reasonable inter-rater reliability.

PRIMARY OUTCOMES: (See appendix for rule) The clinical decision rule adequately identified children at very low risk for IAI-Intervention as evidenced by high sensitivity 97%, 95% CI (93.7, 98.9%) and a negative predictive value of 99.9% (99.7-100). 99.9% with a negative rule did not have an IAI-Intervention. 0.1% (1 out of 1,000) with a negative rule would have IAI-Intervention. The large sample size of 12,044 patients results in excellent precision. The rule however had a low specificity: 42.5%, 95% CI (41.6, 43.4%). Only 42.5% of the patients without an IAI-Intervention were correctly identified if the rule was negative. Whether the tradeoff in specificity for a high sensitivity is justifiable is a judgment call.

The rule appears to be sensible and easy to apply. It has a reasonable number of criteria (7), the predictors are objective and reproducible and the predictors are based on existing clinical practice.

The use of the rule could potentially decrease resource utilization. 42.5% of the patients were considered negative by the rule. The impact of the rule on resource utilization will likely depend on the baseline CT rate. The authors state that it is not their intent that a patient with any of the predictors necessarily require a CT scan. Application of the rule as simply positive or negative could result in an increased rate of CT utilization.

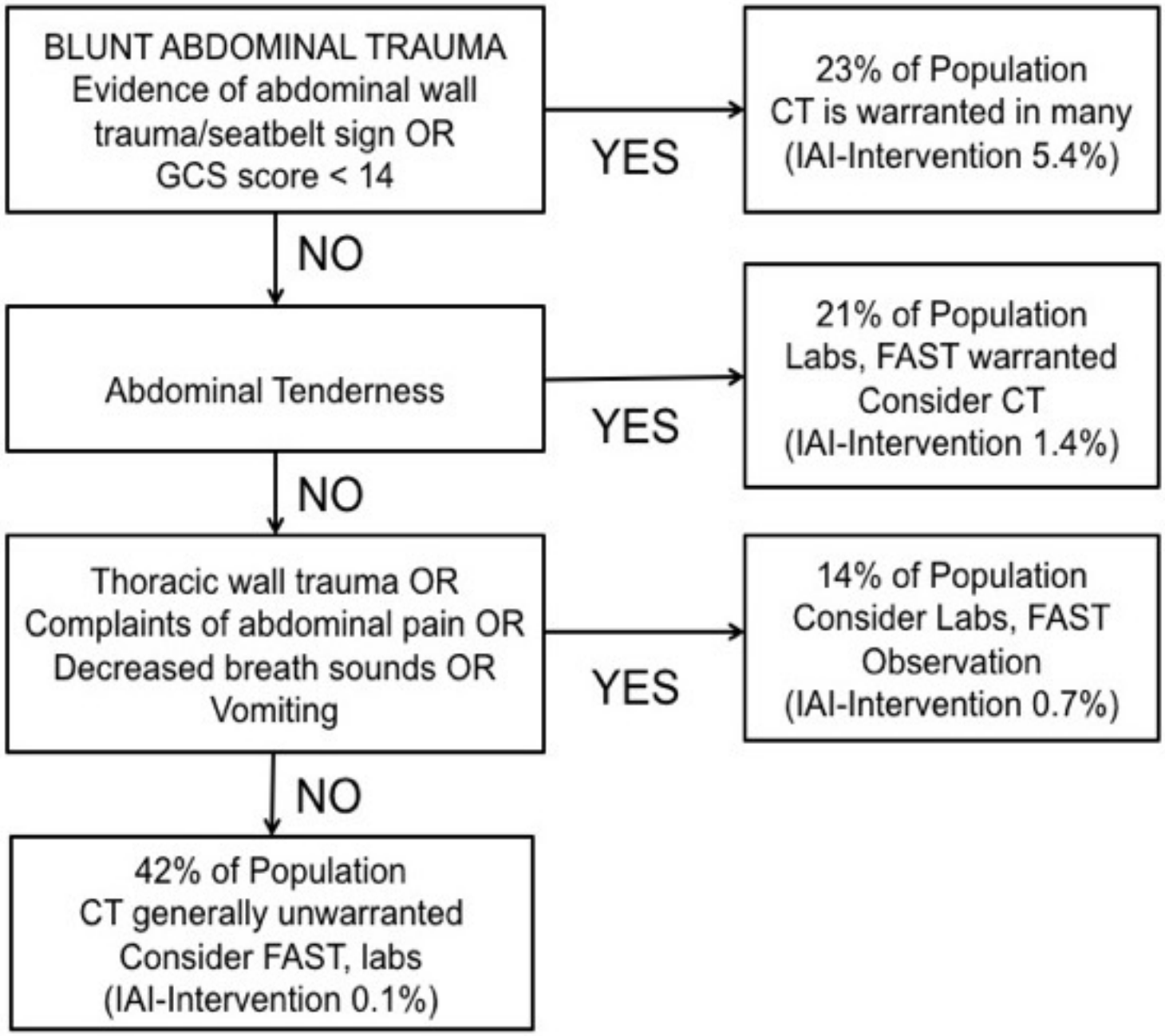
APPLICABILITY: The rule appears to be generalizable to a large variety of children, though the applicability to non-ED and less pediatric specialized ED settings is unclear. This a stage IV decision rule. The rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. Stage IV rules require further validation before it can be applied clinically.

This rule would perhaps have been improved if the results of the bedside FAST (Focused Assessment Sonography for Trauma) exam and/or basic screening laboratory testing (e.g. urinalysis for hematuria, transaminases for liver injury, etc.) were included as predictors. Inclusion of these tests as predictors may have improved the sensitivity, as the 6 patients missed by the clinical decision rule all had abnormalities that may have been identified by these studies.

AUTHOR'S CONCLUSION: "In summary, a prediction rule consisting of 7 patient history and physical examination variables and without laboratory or ultrasonographic information identifies a population of children with blunt torso trauma at very low risk for intra-abdominal injury undergoing acute intervention. These findings require external validation before implementation."

POTENTIAL IMPACT: The clinical decision rule derived in this study has great potential for identification of children at very low risk for IAI-Intervention, but it must be validated and its impact on physician practice, patient risk and outcomes, and resource utilization remains to be determined.

APPENDIX: PECARN RULE SUGGESTED MANAGEMENT



APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	1. ≥ 1 prospective validation in population separate from derivation set 2. Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	1. Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. 2. No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	1. Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	1. Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

ABDOMINAL TRAUMA:
PAIN AND EXAMINATION ACCURACY

In patients under 18 years of age with blunt torso trauma, how accurate is a patient history of abdominal pain and a physical exam finding of abdominal tenderness in detecting intraabdominal injury (IAI) and intraabdominal injury undergoing acute intervention (IAI-AI)?
Does the accuracy of abdominal pain and tenderness vary with a Glasgow Coma Scores between 13-15?

Kelsey Fawcett, MD., Joshua Beiner, MD
January 2018

Adelgais KM, Kuppermann N, Kooistra J, Garcia M, Monroe DJ, Mahajan P, Menaker J, Ehrlich P, Atabaki S, Page K, Kwok M, Holmes JF;
Intra-Abdominal Injury Study Group of the Pediatric Emergency Care Applied Research Network (PECARN).

ACCURACY OF THE ABDOMINAL EXAMINATION FOR IDENTIFYING CHILDREN WITH BLUNT INTRA-ABDOMINAL INJURIES

J Pediatr. 2014 Dec;165(6):1230-1235.e5.
PubMed ID: 25266346

STUDY DEFINITIONS	
POPULATION	Inclusion: <18 years old who sustained blunt torso trauma and presented to the ED within 24 hours with 1 or more of the following: 1. GCS <15 with blunt torso trauma 2. Blunt trauma with paralysis, multiple, nonadjacent long bone fractures, 3. Blunt torso trauma due to MVC ≥ 45 mph with rollover, ejection, automobile ≥ 5 mph versus pedestrian, bicyclist, fall > 20 feet, crush injury to the torso, physical assault involving the abdomen 4. Physician concern for abdominal trauma resulting in abdominal CT, ultrasound (FAST), laboratory testing, chest or pelvic radiography Exclusion: Penetrating trauma, existing neurologic disorder preventing reliable examination, known pregnancy, transfer from another hospital after a previous abdominal CT scan and/or diagnostic peritoneal lavage, initial GCS score of < 13. Setting: Multicenter, 20 PECARN centers, 5/2008-1/2010
TEST	Standardized data collection form including data on: 1. Abdominal Pain (> 2 years) a. Presence: Present or Absent b. Severity: Mild (pain score 1-3), Moderate (4-6), Severe (7-10), Unknown c. Localization: Diffuse, localized, unknown 2. Abdominal Tenderness a. Presence: Present or Absent b. Degree: Mild (pain score 1-3), Moderate (4-6), Severe (7-10), Unknown c. Localization: Periumbilical, supra-umbilical, infra-umbilical, Unknown d. Peritoneal signs: rebound or cough tenderness e. Abdominal distention: Present or Absent f. Bowel sounds: Present or Absent g. Rectal exam (if performed): (+) = gross blood or hemoccult (+)
REFERENCE STANDARD	CT scan of abdomen/pelvic at MD discretion Clinical follow-up of patients without imaging: Review of inpatient medical records, Phone follow-up ≥ 7 days or mailed questionnaire or review of medical/local morgue records Intra-Abdominal Injury (IAI): Radiographic or surgical injury to spleen, liver, urinary tract (from the kidney to the urinary bladder), gastrointestinal tract (including the bowel or associated mesentery from the stomach to the sigmoid colon), pancreas, gallbladder, adrenal gland, intra-abdominal vascular structure, or traumatic fascial defect (traumatic abdominal wall hernia) Intra-Abdominal Injury with Acute Intervention (IAI-AI) 1. Death caused by the intra-abdominal injury 2. Therapeutic intervention at laparotomy 3. Angiographic embolization to treat bleeding from the intra-abdominal injury 4. Blood transfusion for anemia due to hemorrhage from the intra-abdominal injury 5. Administration of intravenous fluids for 2 or more nights in patients with pancreatic or gastrointestinal injuries.
OUTCOME	Relative Risk and Test Characteristics for abdominal pain and tenderness Stratified by Glasgow Coma Scale
DESIGN	Observational: Prospective Cohort (planned secondary analysis)

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. All patients in the study had a history of recent blunt torso trauma for which imaging had not been yet been obtained to confirm or rule out the diagnosis of intraabdominal injury. The patients in the study consisted of a wide range of ages (< 18 years) and varying mechanisms of injury.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The reference standard for the identification of IAI was CT scan or clinical follow up. Clinical follow-up of patients without imaging included: a review of inpatient medical records, Phone follow-up ≥ 7 days, mailed questionnaire or review of medical/local morgue records. The proportion who did not have a CT scan that were available for follow up was not presented.
Were those interpreting the test and reference standard blind to the other results?	Yes. The standardized data collection form was completed prior to imaging if obtained. It is unclear whether those assessing the outcome events (IAI and/or IAI-AI Intervention) were blinded to the presence of the predictors. The radiologists reading the abdominal CT to assess for IAI may have been blinded. It is highly unlikely that the pediatric surgeons, interventional radiologists, and other care providers performing acute interventions were blinded to presence of predictors. However, it is unlikely that knowledge of the predictors would affect the objective outcomes.
Did all investigators perform the same reference standard to all patients regardless of the results of the test under investigation?	No. CT scan of abdomen/pelvic and need for laparotomy were at MD discretion. Clinical follow up served as the reference standard for those not undergoing imaging. It would be unethical to subject all patients to imaging and/or laparotomy.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 11,277, Median 11.3 years (IQR 6.1, 5.1 years), 61% male
Mechanism: MVC (32%), Fall (20%), Struck by vehicle (19%), Bicycle fall/collision (7%)
GCS: 15 (92%), 14 (5.9%), 13 (2.1%)
Rate of IAI without abdominal pain or abdominal tenderness:
- GCS 15: 2%, 95% CI (1, 2%)
- GCS 14: 4%, 95% CI (3, 6%)
- GCS 13: 9%, 95% CI (5, 14%)

RATE OF IAI AND IAI-AI

	GCS 15	GCS 14	GCS 13
IAI	5.4% (5.0, 5.8%)	8.0% (6.0, 10.3%)	11.6% (7.8, 16.5%)
IAI-AI	1.1% (90.9, 1.3%)	3.5% (2.2, 5.1%)	3.0% (1.2, 6.1%)

IAI AND ABDOMINAL PAIN: GCS 15 (PATIENT ≥ 2 YEARS)

	IAI	No IAI	
Any Abdominal Pain: YES	425	2,978	3,403
Any Abdominal Pain: NO	111	5,955	6,066
	536	8,933	9,469

TEST CHARACTERISTICS: ABDOMINAL PAIN: GCS 15 (PATIENT ≥ 2 YEARS)

Prevalence IAI	536/9,469	5.7% (5.2, 6.2%)
Sensitivity	425/536	79.3% (75.7, 82.5%)
Specificity	5,955/8,933	66.7% (65.7, 67.6%)
Predictive Value Negative Test	5,955/6,066	98.2% (97.8, 98.5%)
Predictive Value Positive Test	425/3,403	12.5% (11.4, 13.6%)
Likelihood Ratio Negative Test	(111/536)/(5,955/8,933)	0.31 (0.26, 0.37)
Likelihood Ratio Positive Test	(425/536)/(2,978/8,933)	2.38 (2.26, 2.52)

IAI AND ABDOMINAL TENDERNESS: GCS 15 (ALL PATIENTS)

	IAI	No IAI	
Any Abdominal Tenderness: YES	439	2,951	3,390
Any Abdominal Tenderness: NO	117	6,736	6,853
	556	9,687	10,243

TEST CHARACTERISTICS: ABDOMINAL TENDERNESS: GCS 15 (ALL PATIENTS)		
Prevalence AIA	556/10,243	5.4% (5.0, 5.8%)
Sensitivity	439/556	79% (75.4, 82.1%)
Specificity	6,736/9,687	69.5% (68.6, 70.4%)
Predictive Value Negative Test	6,736/6,853	98.3 (98.0, 98.6%)
Predictive Value Positive Test	439/3,390	12.9% (11.9, 14.1%)
Likelihood Ratio Negative Test	(117/556)/(6,736/9,687)	0.30 (0.26, 2.73)
Likelihood Ratio Positive Test	(439/556)/(2,951/9,687)	2.59 (2.46, 2.73)

TABLE IV
1. Sensitivity decreases with decreasing GCS
2. Severe abdominal pain or tenderness is associated with an increased relative risk of IAI

ANY ABDOMINAL PAIN ((PATIENTS ≥ 2 YEARS): IAI STRATIFIED BY GCS			
	GCS 15	GCS 14	GCS 13
SN	79.3% (75.7, 82.5%)	51% (37.7, 64.1%)	31.8% (16.4, 62.7%)
SP	66.7% (65.7, 67.6%)	77.3% (73.3, 80.9%)	83.3% (76.8, 88.3%)
PV(-)	98.2% (97.8, 98.5%)	93.6% (90.7, 95.6%)	90% (84.2, 93.8%)
PV(+)	12.5% (11.4, 13.6%)	19.5% (13.7, 27.1%)	20.6% (10.3, 36.8%)
LR(-)	0.31 (0.26, 0.37)	0.64 (0.48, 0.82)	0.82 (0.61, 1,10)
LR(+)	2.38 (2.26, 2.52)	2.25 (1.64, 3.09)	1.90 (0.95, 3.85)

ANY ABDOMINAL TENDERNESS (ALL PATIENTS): IAI STRATIFIED BY GCS			
	GCS 15	GCS 14	GCS 13
SN	79% (75.4, 82.1%)	56.6% (43.3, 69.0%)	37% (21.5%, 55.8%)
SP	69.5% (68.6, 70.4%)	80% (76.6, 83.0%)	83.1% (77.3, 87.6%)
PV(-)	98.3 (98.0, 98.6%)	95.5% (93.3, 97.0%)	90.8% (85.7, 94.2%)
PV(+)	12.9% (11.9, 14.1%)	19.9% (14.3, 26.9%)	22.7% (12.8, 37.0%)
LR(-)	0.30 (0.26, 2.73)	0.54 (0.39, 0.74)	0.76 (0.56, 1.02)
LR(+)	2.59 (2.46, 2.73)	2.83 (2.13, 3.76)	2.19 (1.28, 3.91)

Table V: Accuracy of Abdominal Pain and Tenderness Stratified by GCS for AIA-AI
Results similar to those for AIA. Sensitivity decreased with decreasing GCS and risk increases with increased severity of abdominal pain or tenderness

SENSITIVITY FOR AIA-ACUTE INTERVENTION			
	GCS 15	GCS 14	GCS 13
Any Abdominal Pain	80.7% (72.3, 87%)	60.9% (40.8, 77.8%)	50.0% (18.8, 81.2%)
Any Abdominal Tenderness	81.3% (73, 87.4%)	73.9% (53.5, 87.5%)	71.4% (35.9, 91.8%)

TABLE VIII: Isolated Abdominal Pain and/or Tenderness

	IAI	IAI-AI
Isolated Abdominal Pain	3%	1%
Isolated Abdominal Tenderness	6%	1%
Isolated Abdominal Pain or Tenderness	8%	1%

Table IX: Recursive Partitioning
Abdominal pain and abdominal tenderness were independent predictors of IAI with increasing severity associated with higher risk
Abdominal tenderness (and not abdominal pain) was an independent predictor of IAI-AI with increasing severity associated with high risk

HOW CAN I APPLY THE RESULTS TO PATIENT CARE

Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	The authors of the study were careful to only include predictors in the original rule that had reasonable inter-rater reliability. All predictors in the clinical decision rule had kappa values of > 0.6, with the lower bound of the confidence intervals > 0.4. The specific kappa for abdominal tenderness was 0.74 with a lower limit of 0.69 (presented in a separate publication).
Are the study results applicable to the patients in my practice?	Yes. While we do not see a large volume of blunt torso trauma in our institution, the results of this study suggest that in a patient with a normal GCS (15), complaints of abdominal pain and findings of abdominal tenderness of physical exam, should raise high suspicion for intraabdominal injury and should prompt further investigations. In contrast, in a patient with blunt torso trauma, with a GCS of 15 who has no abdominal pain or abdominal tenderness, it is less likely that that patient would have intraabdominal injury and thus does not warrant further work-up.
Will the test results change my management strategy?	Yes. This study will hopefully provide strong evidence for practitioners to incorporate on history and physical exam findings in the diagnose of intraabdominal injury in the setting of blunt torso trauma and not proceed with unnecessary imaging.
Will patients be better off as a result of the test?	Yes. Patients with a GCS < 15 or those with severe abdominal pain or tenderness can be targeted for imaging. In patients with a GCS of 15 with minimal or no tenderness or pain a CT scan can be avoided and the patient undergo serial physical examination and or point of care FAST examination

CLINICAL BOTTOM LINE

BACKGROUND: Torso trauma is the second leading cause of death among children after head injury. While CT scan is a reliable diagnostic test to diagnose intraabdominal injury, it is associated with an increased the risk of radiation-induced malignancy later in life. The Pediatric Emergency Care Applied Research Network (PECARN) derived a clinical prediction rule to identify children who have sustained blunt torso trauma at low risk for intraabdominal injury (Ann Emerg Med. 2013, PubMed ID: 23375510). The prediction rule includes the following parameters: No evidence of abdominal wall trauma or presence of a seat-belt sign, GCS >13, no abdominal tenderness, no thoracic wall trauma, no complaints of abdominal pain, no decreased breath sounds, and no vomiting (See appendix). Patients without any of the 7 criteria of the prediction rule are considered to be of low risk for intraabdominal injury requiring an acute intervention (See Appendix).

CLINICAL QUESTION: In patients under 18 years of age with blunt torso trauma, how accurate is a patient history of abdominal pain and a physical exam finding of abdominal tenderness in detecting intraabdominal injury (IAI) and intraabdominal injury undergoing acute intervention (IAI-AI)? Does the accuracy of abdominal pain and tenderness vary with a Glasgow Coma Scores between 13-15?

DESIGN/RISK OF BIAS: This study was a secondary analysis of a large, multicenter, prospective, observational study conducted between May 2008 and January 2010 in 20 different PECARN pediatric emergency departments. This was a well-designed study that included 11,277 patients. Complaints of abdominal pain are unique to each patient and tends to be very subjective. Similarly, abdominal tenderness on physical exam and the degree of abdominal tenderness are also very subjective. The investigators attempted to reduce the subjectivity by using a standardized data collection form and included only predictors in the clinical decision rule that had kappa values of > 0.6, with the lower bound of the confidence intervals > 0.4. The kappa for abdominal tenderness was 0.74 with a lower limit of 0.69 (PubMed ID: 23672355). The accuracy of abdominal pain and tenderness was stratified by Glasgow Coma Scale. It may have been helpful to determine the accuracy based on age as these findings may be more difficult to assess in younger children.

PRIMARY RESULTS: The most common mechanism of injury was a motor vehicle collision and 92% had a GCS of 15. Patients with no abdominal pain or tenderness had a rate of intraabdominal injury of 2%, 95% CI (1, 2%). This study showed that with decreasing GCS scores, the sensitivity of abdominal pain and abdominal tenderness in intraabdominal injury decreased. The sensitivity of abdominal pain with a GCS of 15 was 79%, 95% CI (76, 84%) and decreased to 32%, 95% CI (14, 55%) with a GCS of 13. Similarly, the sensitivity of abdominal tenderness with a GCS of 15 was 79%, 95% CI (75, 82%) and decreased to 37%, 95% CI (19, 58%) with a GCS of 13. The risk of IAI was highest in patients with severe abdominal pain and tenderness at all GCS levels. The results for IAI-AI were similar. However, the statistical significance of the decrease in sensitivity by GCS and severity was not presented. The study also demonstrated that diffuse abdominal pain, tenderness, absent bowel sounds, peritoneal irritation, and abdominal distention were all associated with the presence of intraabdominal injury.

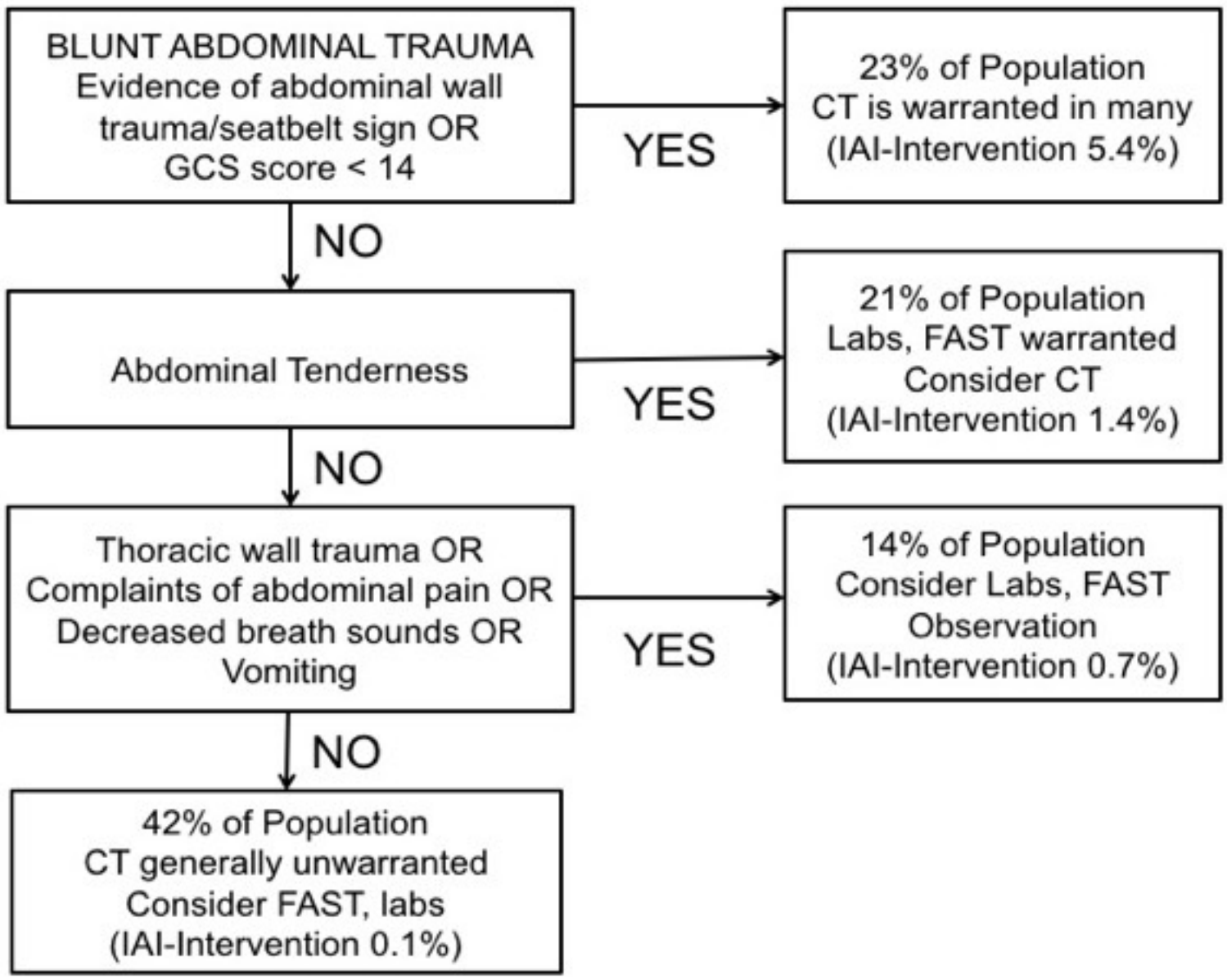
APPLICABILITY: This was a multicenter study whose results are likely generalizable to the children's hospital setting and patients meeting the studies inclusion and exclusion criteria. If applied to our practice, this study could potentially reduce the amount of abdominal CT scans that are being ordered on children with torso trauma, a normal GCS and without abdominal pain or tenderness. In patients with an abnormal GCS or concerning physical exam findings, further investigations would be appropriate.

Due to the small number of patients with GCS 14 and 13 the confidence intervals are very wide. Extrapolation of the study's results to these patients may not be valid.

AUTHOR'S CONCLUSION: "In conclusion, most children with IAI and normal mental status will complain of abdominal pain and have findings of abdominal tenderness on examination. Furthermore, the risk of IAI increases as the degree of abdominal findings increases. The sensitivity of abdominal pain and tenderness in children with IAI decreases as the GCS score decreases. Although abdominal CT is not mandatory, the risk of IAI is sufficiently high to warrant diagnostic evaluation of children with isolated abdominal pain and/or tenderness after blunt torso trauma."

POTENTIAL IMPACT: A complaint of abdominal pain and or a finding of abdominal tenderness can be used to the determine the likelihood or IAI and IAI-AI and guide further evaluation. However, not all will agree that sensitivities in the high 70's to low 80% for these outcomes are "good". Patients with a GCS of less than 15 and in particular those with severe pain or tenderness were at increased risk of IAI and IAI-AI and likely require additional evaluation. Patients with a GCS of 15 with low or moderate severity of pain or tenderness and without other indication for imaging could potentially be monitored with laboratory testing, serial ultrasound and serial exams.

APPENDIX: PECARN ABDOMINAL TRAUMA DECISION RULE



CERVICAL SPINE INJURY:
ADULT NEXUS CRITERIA VALIDATION

In blunt trauma patients for which cervical spine XRAYs are ordered are the National XRAY Utilization Study (NEXUS) criteria accurate in identifying those with and without a cervical spine injury?

Michael Mojica, M.D.
January 2017

Hoffman JR, Mower WR, Wolfson AB, Todd KH, Zucker MI.

VALIDITY OF A SET OF CLINICAL CRITERIA
TO RULE OUT INJURY TO THE CERVICAL SPINE
IN PATIENTS WITH BLUNT TRAUMA

N Engl J Med. 2000 Jul 13;343(2):94-9.
PubMed: 10891516

STUDY DEFINITIONS	
POPULATION	Inclusion: Blunt trauma patients, cervical spine XRAYS ordered Exclusion: Penetrating trauma, C-spine XRAYS for a non-trauma indication Setting: 21 centers (academic/community, public/private, with/without residency, small/large, varying levels of trauma certification), enrollment period not specified
INTERVENTION	NEXUS Cervical spine rule criteria: absent, present, unable to assess 1. No midline cervical tenderness 2. No focal neurologic deficit 3. Normal alertness 4. No intoxication 5. No painful, distracting injury Site liaison investigators underwent 1 hour of training in the implementation of the rule and then trained site clinicians either formally or informally
CONTROL	Cervical spine injury: Clinically or not clinically significant Not clinically significant defined as injuries requiring no treatment and are not expected to result in harm. Isolated (no other bone injury), no evidence of ligamentous injury or spinal cord injury C-spine XRAY (cross table lateral, anterior-posterior, open-mouth (odontoid). CT or MRI could have been ordered if plain XRAYS were impractical/ impossible.
OUTCOME	Rule characteristics Potential reduction in XRAY utilization
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were the patients chosen in an unbiased fashion and do they represent a wide spectrum of severity of disease?	Unclear. All patients with blunt trauma for which C-spine XRAYS were ordered were included. This was a multicenter study and indications for XRAY utilization in blunt trauma were not pre-defined by the study. Patient characteristics other than an age range and gender are not presented.
Was there a blinded assessment of the criterion standard for all patients?	Yes. Radiologists interpreting the XRAY were masked to the rule criteria. Final interpretation of the XRAY was by a designated radiologist. If the radiology report was ambiguous the designated radiologist reviewed both the report and the XRAY.
Was there an explicit and accurate interpretation of the predictor variables and the actual rule without knowledge of the outcome?	Yes. Clinicians completed the assessment of the rule criteria before the results of XRAYS were available. The rule criteria were not explicitly defined. This was intentional. The authors state that this was done because “the criteria could not be precisely defined in a clinically meaningful way” and extensive definitions would impede usability of the rule. Examples of possible interpretations were reviewed during training and were available on a site computer.
Was there 100% follow up of those enrolled?	Unclear. All patients were followed until XRAY results were available. No effort was made to contact patients after discharge. Neurosurgical records were reviewed for 3 months to identify missed injuries.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

N = 34,069, mean age: 40 years, 58.7% male
Any cervical spine injury: 818/34,069 = 2.4%
Clinical significant cervical spine injury: 578/34,069 =1.7%
Proportion CSI clinically significant: 578/818 = 70.6%

ANY CERVICAL SPINE INJURY

		CERVICAL SPINE INJURY		
		YES	NO	
NEXUS RULE	POSITIVE	810	28,950	29,760
	NEGATIVE	8	4,301	4,309
		818	33,251	34,069

Prevalence: 818/34,069 = 2.4%
Sensitivity: 810/818 = 99%, 95% CI (98, 99.6%)
Predictive Value (-) Rule: 4,301/4,309= 99.8%, 95% CI (99.6,100%)
Specificity: 4,301/33,251 = 12.9%, 95% CI (12.8, 13.0%)
Predictive Value (+) Rule: 810/29,760 = 2.7%, 95% CI (2.6, 2.8%)

CLINICALLY SIGNIFICANT CERVICAL SPINE INJURY

		CERVICAL SPINE INJURY		
		YES	NO	
NEXUS RULE	POSITIVE	576	29,184	29,760
	NEGATIVE	2	4,307	4,309
		578	33,493	34,069

Prevalence: 578/34,069 = 1.7%
Sensitivity: 576/578 = 99.6%, 95% CI (98.6, 100%)
Predictive Value (-) Rule: 4,307/4,309 = 99.9%, 95% CI (99.8,100%)
Specificity: 4,307/33,493 = 12.9%, 95% CI (12.8, 13%)
Predictive Value (+) Rule: 576/29,760 = 1.9%, 95% CI (1.8, 2.0%)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

88.4% (29,760/34,069) had a positive rule and would have an XRAY performed if the rule was used in a directive manner. Since 100% of the patients in the study had XRAYs, use of the rule would have potentially decreased the rate of XRAY by 11.6% (100% - 88.4%)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see appendix)	☐ I ■ II ☐ III ☐ IV This is level II clinical decision rule. A level II rule has been validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. An impact analysis has not been completed. A level II rule can be used rule in a wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve.
Does the rule make clinical sense?	Yes. The rule makes clinical sense. The rule parameters are those that are typically used to assess for the possibility for cervical spine injury. An exception is a parameter for mechanism of injury is not included.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. The authors provide a range of inter-rater reliability (kappa statistic) of 0.58-0.86 for the rule criteria but do not report inter-rater reliability each criteria. Inter-rater reliability for the rule as a whole (rule positive vs rule negative) was good (kappa 0.73).
Is the rule applicable to the patients in my practice?	This rule included patients of all ages. There were 3,065 patients included less than 18 years of age. Of these only 817 patients were less than or equal to 8 years of age and 88 less than 2 years of age. Only 4 cervical spine injuries occurred in those 2-9 years or age and none less than 2 years. See PEMCAR: Pediatric NEXUS
Will the rule results change my management strategy?	Yes. The rule is used currently in adolescent patients to assess for the need for cervical spine XRAY?
What are the benefits of applying the rule to my patients?	The potential benefit of the use of the rule is a reduction in those requiring XRAYS. In the study population 11.6% of the patients were considered negative and potentially could have avoided XRAY. An impact analysis of the rule is necessary to assess that actual reduction in XRAY utilization.
What are the risks of applying the rule to my patients?	The greatest potential risk is in missing a patient with a clinically significant cervical spine injury who could then be at risk of a spinal cord injury. Only 2 patients with clinically significant cervical spine injuries were considered rule negative (see article results section for a description of these 2 patients). The lower limit of the 95% confidence interval for the predictive value of a negative rule for clinically significant cervical spine injury is 99.8%. Potentially 0.2% (1 in 500) of patients with a clinically important cervical spine injury could be considered rule negative.

CLINICAL BOTTOM LINE

BACKGROUND: The rate of cervical spine injury in blunt trauma patients is low. Missing a patient with a cervical spine injury can have devastating effects so that cervical spine XRAYs are frequently ordered and are normal a very high percentage of the time. A clinical decision rule that could identify clinical characteristics of those at low risk for a cervical spine injury could potentially decrease cervical spine XRAY utilization in blunt trauma patients.

CLINICAL QUESTION: In blunt trauma patients for which cervical spine XRAYs are ordered are the National XRAY Utilization Study (NEXUS) criteria accurate in identifying those with a cervical spine injury?

DESIGN/RISK OF BIAS: This was a well-designed prospective cohort of patients with blunt trauma for which cervical spine XRAY's were ordered. The study was performed to assess the validity of the NEXUS criteria and included 34,069 patients. There was little description of the patient population other than an age range and gender proportions. The indication for XRAY were not specified. No effort was made to contact patients after discharge though neurosurgical records were reviewed for 3 months to identify missed injuries.

PRIMARY RESULTS: 2.4% of patients had cervical spine injury while 1.7% had a clinically significant cervical spine injury. The rule was accurate identifying those with any cervical spine injury (Sensitivity: 99%, 95% CI (98, 99.6%), Predictive Value of a Negative Rule: 99.8%, 95% CI (99.6, 100%). For any cervical spine injury, the rule stratified patients with a baseline risk of cervical spine injury of 2.4% into a low risk group (CSI rate 0.2%) if the rule was negative and a high risk group (CSI rate = 2.7%) if the rule was positive.

The rule was also accurate for the identification of clinically significant cervical spine injury as well (Sensitivity: 99.6%, 95% CI (98.6, 100%), Predictive Value of a Negative Rule: 99.9%, 95% CI (99.8,100%). For clinically significant cervical spine injury, the rule stratified patients with a baseline risk of cervical spine injury of 1.7% into a low risk group (CSI rate = 0.2%) if the rule was negative and a high-risk group (CSI rate = 1.9%) if the rule was positive.

88.4% of patients had a positive rule and would have an XRAY performed. Since 100% of the patients in the study had XRAYs, use of the rule would have potentially decreased the XRAY rate by 11.6%.

NEXUS CERVICAL SPINE RULE CRITERIA*		
NO	N	Neurologic deficit (focal)
	S	Spinal Tenderness (midline)
	A	Altered Mental Status
	I	Intoxication
	D	Distracting injury (painful)
*Rule criteria evaluated as: Absent, present, unable to assess If unable to assess, the criteria is considered present and XRAYS are indicated		

APPLICABILITY: The use of 21 hospitals with varying characteristics likely make the study's results generalizable to the majority of patients with blunt trauma in which a cervical spine injury is suspected. The authors provide a range of inter-rater reliability of 0.58-0.86 for the rule criteria but do not specify the statistic each criteria individually. Inter-rater reliability for the rule as a whole (rule positive vs rule negative) was good (kappa 0.73).

The rule criteria were not explicitly defined. This was intentional. The authors state that this was done because "the criteria could not be precisely defined in a clinically meaningful way" and extensive definitions would impede usability of the rule.

This is level II clinical decision rule. A level II rule has been validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. An impact analysis has not been completed. A level II rule can be used rule in a wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve.

AUTHOR'S CONCLUSION: "In summary, this prospective, multicenter study confirms the validity of a decision instrument based on five clinical criteria for identifying, with a high degree of confidence, patients with blunt trauma who have an extremely low probability of having sustained injury to the cervical spine. The sensitivity of this set of criteria approaches 100 percent for clinically important injuries, and its general application should result in both clinical and economic benefit. As with any other clinical tool, it should be applied with great care and should not replace clinical judgment in the care of individual patients. There may be compelling reasons to order cervical-spine images in individual cases, even if all the criteria for a low probability of injury are met."

POTENTIAL IMPACT: This was a well designed study that has the potential to decreased XRAY utilization. An impact analyses is required to determine that actual rate of reduction. The potential for rarely missing a patient with a clinically significant cervical spine injury should be considered and factors other than the rule criteria (such as a high risk mechanism of injury e.g. diving) may also aid in the decision to obtain cervical spine XRAYs.

APPENDIX: CLINICAL DECISION RULE STAGE

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

CERVICAL SPINE INJURY:
CONSENSUS BASED DECISION ALGORITHM

In pediatric patients with blunt trauma and a suspected cervical spine injury who have not undergone advanced imaging (CT or MRI) what is the diagnostic accuracy of a consensus-based cervical spine clearance algorithm?

Michael, Mojica, M.D.
January 2017

Arbuthnot M, Mooney DP.

THE SENSITIVITY AND NEGATIVE PREDICTIVE VALUE OF A PEDIATRIC CERVICAL SPINE CLEARANCE ALGORITHM THAT MINIMIZES COMPUTERIZED TOMOGRAPHY

J Pediatr Surg. 2017 Jan;52(1):130-135.
PubMed ID: 27908536

STUDY DEFINITIONS	
POPULATION	Inclusion: < 21 years, cervical spine evaluation, seen in ED directly from the scene or in transfer, in a c-collar, without prior advanced imaging (CT/MRI) Exclusion: None specified Setting: Single Children's Hospital ED (Level 1 Trauma Center), 1/2005-8/2015
INTERVENTION	Application of a cervical spine decision algorithm (See Appendix): Performed by ED fellow or attending or senior general surgery resident or surgical critical care fellow in conjunction with a pediatric general surgery attending.
CONTROL	Cervical spine imaging study: No imaging, plain films, CT, MRI Cross section Imaging (CT, MRI) decision made in consultation with "spine consult" (pediatric neurosurgery or pediatric orthopedics)
OUTCOME	Algorithm characteristics Subgroup analysis of those < 3 years of age
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were the patients chosen in an unbiased fashion and do they represent a wide spectrum of severity of disease?	Unclear. Limited patient characteristics are presented. Patients were seen primarily or transferred to an academic medical center that is a level 1 trauma center.
Was there a blinded assessment of the criterion standard for all patients?	Unclear. It is unclear if those interpreting the imaging studies were aware of patient clinical characteristics. They were likely aware of the result of prior imaging studies (e.g. plain XRAY results prior to CT)
Was there an explicit and accurate interpretation of the predictor variables and the actual rule without knowledge of the outcome?	Yes. Application of the algorithm was applied without knowledge of the presence or absence of imaging findings. Knowledge of plain XRAY findings could certainly influence the decision to obtain advanced imaging.
Was there 100% follow up of those enrolled?	Unclear. It is unclear if those who underwent clinical clearance or clearance with plain XRAY only were followed after discharge though it is unlikely that a clinical important cervical spine injury would be missed.

WHAT ARE THE RESULTS?

How well did the rule correctly identify patients <u>with</u> the primary outcome? How precise was this measurement? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

How well did the rule correctly identify patients <u>without</u> the primary outcome? How precise was this measurement? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

N = 1,023 (Directly from scene: 56%, transferred 44%)
Cervical Spine Injury (all patients): 18/1,023 (1.8%)
Cervical Spine Injury (< 3 years): 1/135 (0.7%)
All 18 identified on plain XRAY (10 confirmed by CT)

EVALUATION (ALL)	N (%)
Clinical (no imaging)	237 (23.7%)
Plain XRAY alone	688 (67.3%)
CT after Plain XRAY	93 (9.1%)
CT alone	5 (0.5%)
CT rate: (93+5)/1,023 = 9.6%	

EVALUATION (< 3 YEARS)	N (%)
Clinical (no imaging)	43 (31.9%)
Plain XRAY alone	91 (67.4%)
CT after Plain XRAY	3 (2.2%)
CT alone	1 (0.7%)
CT rate: (3+1)/135 = 3%	

		C-SPINE INJURY		
		YES	NO	
ALGORITHM	POSITIVE	17	0	17
	NEGATIVE	1*	1,052	1,053
		18	1,052	1,070
*1 missed patient: displaced spinous process fracture				

RULE CHARACTERISTIC	CALCULATION	95% CI
Sensitivity	94.4% (17/18)	(72.7, 99.9%)
Specificity	100% (1,052/1,052)	(99.7, 100%)
Predictive Value (+) Rule	100% (17/17)	(80.5, 100%)
Predictive Value (-) Rule	99.9% (1,052/1,053)	(99.5, 100%)
Likelihood Ratio (+) Rule	Not calculable (17/18)/(0/1,052)	
Likelihood Ratio (-) Rule	0.056 (1/18)/(1,052/1,052)	

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?
The impact on resource utilization will depend on the current rate of CT utilization. 9.6% of patients required a CT (3% of those less than 3 years of age).

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

At what level of development is this rule? How can it be applied? (see appendix)	☐ I ☐ II ☐ III ☐ IV ■ Not applicable The algorithm was arrived at by consensus and not derived mathematically from potential predictors.
Does the rule make clinical sense?	Yes. The parameters that make up the algorithm consist of those included in the NEXUS criteria and Canadian c-spine rule as well as plain XRAY imaging findings. The last algorithm parameter “Is there a high suspicion of injury” is very subjective. Mechanism of injury is not included.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. This was a retrospective study so that the reproducibility of the rule cannot be assessed. The clinical expertise and experience of the physicians utilizing the algorithm at level I pediatric trauma center may not be generalizable to other settings. A prospective evaluation of the algorithms accuracy in other settings would be useful. The rate of cervical injury in the study population is consistent with the rate in the literature.
Is the rule applicable to the patients in my practice?	Yes.
Will the rule results change my management strategy?	Not at this time. The algorithm would need to be prospectively validated to ensure its reproducibility and validated in other settings to ensure its generalizability.
What are the benefits of applying the rule to my patients?	The primary benefit of applying the algorithm would be to limit radiation exposure from CT. The CT rate was 9.6% (3% in those less than 3 years of age). It is unclear what the CT rate was prior to implementation of the algorithm.
What are the risks of applying the rule to my patients?	The primary risk of applying the algorithm is the possibility of missing a patient with a cervical spine injury. Only 1 patient with a stable spinous process fracture was missed by the rule. Given the low rate of cervical spine injury (1.8% in the study) a larger sample size would be required to be confident in not missing an injury. The lower limit of the 95% confidence interval for the predictive value of a negative algorithm was 99.5%. This indicates that 0.5% (1 out of 200) of those with a negative rule could potentially have a cervical spine injury.

CLINICAL BOTTOM LINE

BACKGROUND: The rate of pediatric cervical spine injury in blunt trauma patients is low (1-2%). Missing a patient with a cervical spine injury can have devastating effects. CT scans has been increasingly used to evaluate for cervical spine injury but are associated with the potential for adverse effects related to radiation exposure. The risk of subsequent malignancy is highest in younger patients. Anatomic differences in the pediatric cervical spine predispose children to a distinct range of injuries and adult cervical spine clearance algorithms may not be applicable. The use of existing clinical decision rules for pediatric cervical spine injury are limited by sample size (Pediatric NEXUS, Pediatrics 2001, PubMed ID: 11483830) or have not been validated (PECARN, Annals EM 2011, PubMed ID: 21035905).

CLINICAL QUESTION: In pediatric patients with blunt trauma and a suspected cervical spine who have not undergone advanced imaging (CT or MRI) what is the diagnostic accuracy of a consensus-based cervical spine clearance algorithm?

DESIGN/RISK OF BIAS: This is a retrospective cohort study to determine the diagnostic accuracy of a consensus-based cervical spine clearance algorithm (See appendix) that has been utilized at a single Children's Hospital Level 1 trauma center. Importantly, the algorithm was not derived mathematically. The algorithm used a combination of clinical and plain XRAY finding to determine the need for cross sectional imaging (CT or MRI). 1,023 pediatric patients with blunt trauma who were seen in the ED either directly from the scene of in transfer who arrived in a cervical spine collar and who had not undergone advanced imaging (CT or MRI) were included). The study was well designed with limitations inherent to the retrospective design.

PRIMARY RESULTS: The algorithm had a high predictive value of a negative algorithm (99.9%, 95% CI (99.5, 100%). The one patient with a cervical spine injury missed by the algorithm had a clinically non-significant spinous process fracture. Algorithm characteristics for patients less than three years of age were not presented likely due to the small sample size (135 patients with 1 cervical spine injury). Use of the algorithm resulted in a 9.6% CT rate in all patients and a 3% CT rate in those less than three years of age. The reduction in CT usage will depend on the baseline rate of usage.

EVALUATION	ALL PATIENTS (1,023)	PATIENTS < 3 YRS (135)
Cervical Spine Injury	18 (1.8%)	1 (0.7%)
Clinical (no imaging)	237 (23.7%)	43 (31.9%)
Plain XRAY alone	688 (67.3%)	91 (67.4%)
CT after Plain XRAY	93 (9.1%)	3 (2.2%)
CT alone	5 (0.5%)	1 (0.7%)
CT RATE	9.6%	3%

ALGORITHM CHARACTERISTIC	%, (95% CI)
Sensitivity	94.4%, (72.7, 99.9%)
Specificity	100%, (99.7, 100%)
Predictive Value of a Positive Rule	100%, (80.5, 100%)
Predictive Value of a Negative Rule	99.9%, (99.5, 100%)
Likelihood Ratio of a Positive Rule	Not calculable (due to 0)
Likelihood Ratio of a Negative Rule	0.056 (0.008, 0.373)

APPLICABILITY: The use of the algorithm is dependent of clinical experience and expertise. It is unclear if the results from a single pediatric children's hospital can be generalized to other settings. A prospective evaluation of the algorithm's accuracy in other setting would be useful to assess the reproducibility of its components and the generalizability to other settings. The last algorithm parameter "Is there a high suspicion of injury" is very subjective. This assessment likely requires a high degree of expertise though it allows for the incorporation of other parameters into the algorithm such as mechanism or injury. In addition, 4 nodes of the algorithm end at "Get Spine Consult" The spine consults indications for cross-sectional imaging are not specified. It is clear that abnormal plain XRAYS were not the only indication for CT. It is reported that all 31 patients with a cervical spine injury had an abnormal XRAY and yet 93 patients had a CT after plain XRAY.

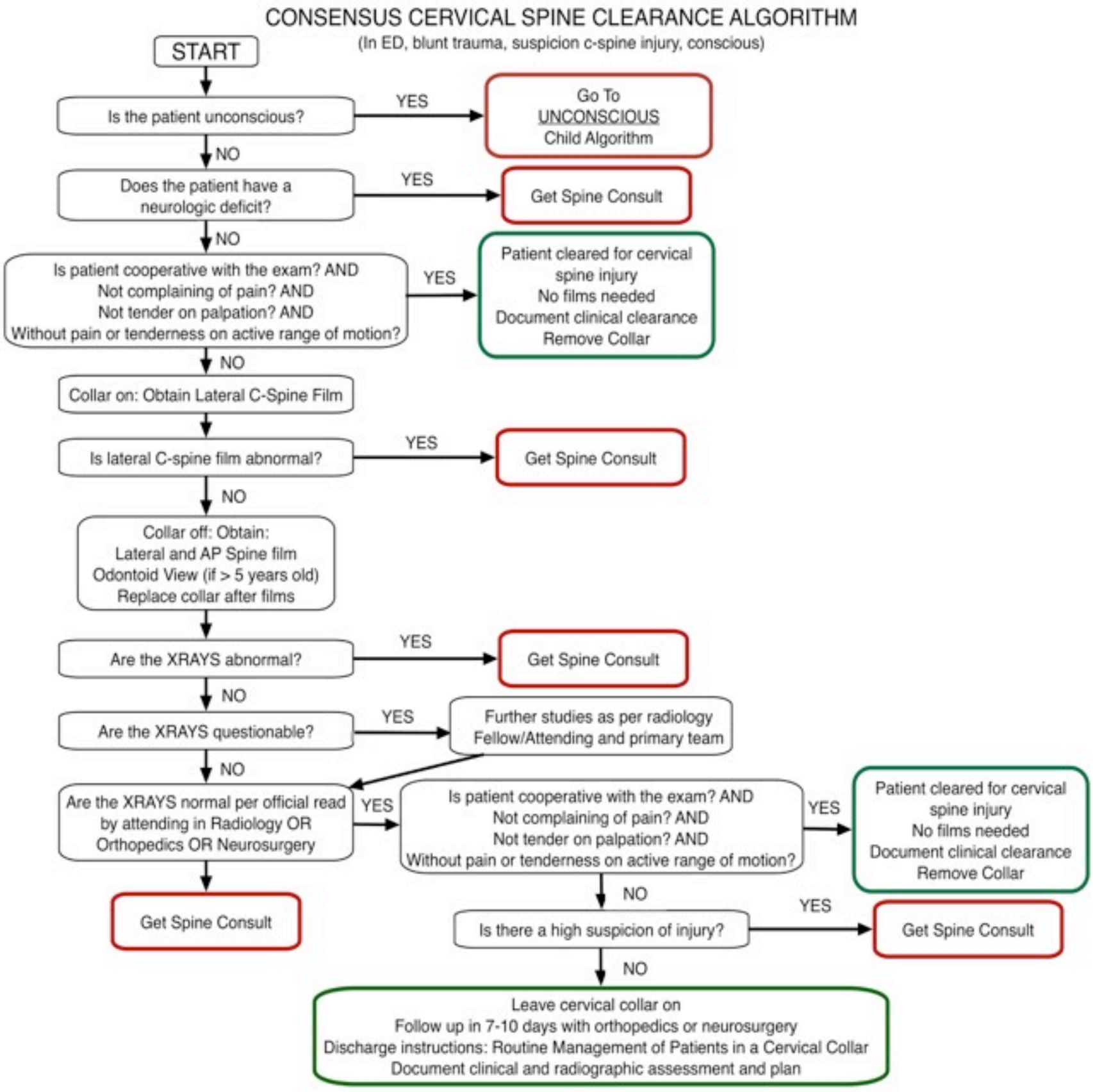
AUTHOR'S CONCLUSION: "In conclusion, although the literature is fraught with guidelines for the clearance of the pediatric cervical spine, there remains great obscurity among providers when it comes to deciding on an appropriate imaging strategy which successfully identifies cervical spine injury while minimizing radiation. Our algorithm relies on expert clinical judgment and screening radiographs, when deemed necessary, to clear the pediatric cervical spine and avoid missed injuries, while reducing the number of cervical spine CTs obtained, and the concomitant risk of malignancy. We have demonstrated that the children in the most radiosensitive population, those less than 3 years of age, can be accurately evaluated while minimizing radiation exposure utilizing this algorithm. The high sensitivity (94.4%) and NPV (99.9%) of our algorithm further support this approach. With the wide application of our algorithm, or one similar, we hope to see the overall rates of pediatric cervical spine CTs decrease, especially in the mixed adult/pediatric trauma centers, while simultaneously maintaining the health and safety of the pediatric patient. Further studies, including the validation of our algorithm by a multi-institutional prospective study, are warranted. Additionally, future studies to determine the optimal age-adjusted imaging study for children at risk for cervical spine injury are justified."

POTENTIAL IMPACT: The use of clinical and plain XRAY in conjunction with a collaborative approach to the use of cross sectional imaging is appealing. A larger prospective study of the algorithms accuracy in a variety of settings would be helpful to generalize the use of the algorithm from a single Children's hospital Level 1 trauma center.

The authors derived their consensus algorithm using principles that warrant repeating.

1. Cervical spine clearance in a child is a clinical event, not a radiologic event
2. Cervical spine clearance is not an emergency. If a child's cervical spine cannot be cleared clinically during the initial evaluation, they remain safely immobilized and are later reevaluated.
3. The rate of cervical spine injury in an alert, neurologically intact child without cervical spine tenderness is likely lower than the rate of subsequent malignancy from radiation exposure.

APPENDIX: ALGORITHM: CONSCIOUS PATIENT



CERVICAL SPINE INJURY: DECISION RULE DERIVATION (PECARN)

In children less than 16 years of age who sustain blunt trauma are clinical signs and symptoms accurate in identifying those who requires cervical spine imaging to identify cervical spine injury and cervical spine injury requiring neurosurgical intervention?

Lili Moran, M.D., Adriana Manikian, M.D.
December 2010

Leonard JC, Kuppermann N, Olsen C, Babcock-Cimpello L, Brown K, Mahajan P, Adelgais KM, Anders J, Borgialli D, Donoghue A, Hoyle JD Jr, Kim E, Leonard JR, Lillis KA, Nigrovic LE, Powell EC, Rebella G, Reeves SD, Rogers AJ, Stankovic C, Teshome G, Jaffe DM;
Pediatric Emergency Care Applied Research Network.

FACTORS ASSOCIATED WITH CERVICAL SPINE INJURY IN CHILDREN AFTER BLUNT TRAUMA

Ann Emerg Med. 2011 Aug;58(2):145-55.
PubMed ID: 21035905

STUDY DEFINITIONS	
POPULATION	Inclusion: Children < 16 years with cervical spine radiography after blunt trauma. Cases: With Cervical spine injury, identified by ICD-9 codes from billing database (injuries to cervical vertebrae, ligaments, or spinal cord and spinal cord injury without radiographic association). Confirmed in medical record. Principal investigator and a pediatric neurosurgeon verified case by reviewing abstracted radiology reports and spine consultation notes. Controls: Without cervical spine injury. 2 controls selected for each case 1. Random controls (1,060) 2. Mechanism of injury controls: matched to age and mechanism (1,012) 3. EMS control: Received EMS out-of-hospital care, matched for age (702) Exclusion: None specified Setting: 17 Children's Hospital EDs in the PECARN Network, 2000-2004
RULE	Standardized, structured chart review by trained research assistants and verified by site investigators (from PECARN hospital, referring hospital and EMS records) Parameters defined from previous literature demonstrating or selected because of biological plausibility.
REFERENCE STANDARD	Cervical spine radiology reports and spine consultation notes
OUTCOME	Rule characteristics Potential decrease in XRAY utilization
DESIGN	Observation: Case-Control (Retrospective)

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. The authors were very thorough, including all factors used in prior studies. See Table 2 for included risk factors.
Were all important predictors present in significant proportion of the study population?	Unclear. This was not stated explicitly. Table 3 shows Odds Ratios, but the original data are not presented.
Were the outcome event and predictors clearly defined?	Yes. The outcome of injury and each predictor was clearly defined.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	No. This was done by chart review, and the cases were picked by presence of absence of c-spine injury. However, data collectors were trained in standard chart review methods, and a second collector was used to review 10% of the charts to ensure that data collection was reliable.
Was the sample size adequate (including an adequate number of outcome events)?	Yes. This study included 540 children with cervical spine injury as cases and 1,060 patients as control in the random controls decision rule. Only 27 cases of cervical spine injury were found in children < 2 years of age

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

At least 1 of 8 parameters (unconditional controls)
(Negative predictive values not calculable in a case-control study)

C-Spine Injury
Sensitivity: 94% (91-96%) Primary site data only
Sensitivity: 98% (96-99%) EMS & transfer data included

C-spine Injury requiring neurosurgical stabilization
Sensitivity: 94% (90-97%) Primary site data only
Sensitivity: 97% (95-98%) EMS & transfer data included

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

At least 1 of 8 parameters (unconditional controls)
(Positive predictive values not calculable in a case-control study)

C-Spine Injury
Specificity: 32%(29-35) Primary site data only
Specificity: 26%(23-29) EMS and transfer data included

C-spine Injury requiring neurosurgical stabilization
Specificity: Not provided

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

The authors state that the rule could potentially reduce exposure to spinal immobilization and ionizing radiation by 25%.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

Yes. The authors performed a boot strap analysis to assess the stability of the selected risk factors. Results of this analysis were similar to the generated decision rules.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see appendix)	☐ I ☐ II ☐ III ■ IV A level IV rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. It requires further validation before it can be applied clinically
Does the rule make clinical sense?	Yes. The risk factors are appropriate and make clinical sense.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Interrater reliability was assessed for data abstraction. It could not be assessed retrospectively for the rule parameters. Despite providing definitions, some of the parameters seem subjective and thus open to interpretation. A table with definitions of the rule parameters should accompany the rule.
Is the rule applicable to the patients in my practice?	Yes. The patients in the study are similar to our patients and could be applied to them if the rule is validated
Will the rule results change my management strategy?	No. The rule requires further validation before it can be applied clinically. However, many of the parameters of the rules are currently used to make imaging decisions.
What are the benefits of applying the rule to my patients?	The primary benefit is a reduction the risk of ionizing radiation and complications of immobilization and sedation. Removing the c-collar may also facilitate further examination of the irate child.
What are the risks of applying the rule to my patients?	The possibility of missing a c-spine injury, resulting in significant disability or death. 11 of 540 (0.02%, 1 in 5,000) patients with cervical spine injury did not have any of the rule parameters and would have been classified as low risk. 1 of 540 (0.002%, 1 in 50,000) of these patients required neurosurgical stabilization at a later date.

CLINICAL BOTTOM LINE

BACKGROUND: Pediatric cervical spine injuries are rare (< 1% after blunt trauma). Decision rules to identify risk of cervical spine injury in adults have been developed (NEXUS criteria, Canadian C-spine rule). The largest pediatric rule was developed as a subset of the Nexus study. (Vicellio, Pediatrics 2001, PubMed ID: 11483830). The pediatric NEXUS included only 30 patients with cervical spine injuries. While the sensitivity of the rule was 100%, the lower limit of the 95% confidence interval was 88% due to the small sample size.

CLINICAL QUESTION: In children less than 16 years of age who sustain blunt trauma are clinical signs and symptoms accurate in determining who does not requires cervical spine imaging to identify cervical spine injury and cervical spine injury requiring neurosurgical intervention?

DESIGN/VALIDITY: This was a multicenter, retrospective case-control study completed by the Pediatric Emergency Care Applied Research Network (PECARN). It is the largest study to date including 540 children with cervical spine injury with 184 requiring neurosurgical stabilization. The goal of the study was to identify clinical factors associated with cervical spine injury in children after blunt trauma. The decision rule was developed using three control groups: random controls, controls match by age and mechanism and controls matched by age and EMS care.

There are a number of validity concerns. First, outcomes were based on XRAY readings and not review of the actual XRAYS. Plain films were used and not CT scans of the cervical spine. The prevalence of injury cannot be determined in a case-control study.

PRIMARY RESULTS: A combination of eight parameters representing past medical history, mechanism of injury, patient's complaint and physical exam findings were found to be predictive of cervical spine injury. A positive rule was defined as the presence of any 1 of the 8 rule parameters. A negative rule was defined as the absence of all 8 of the parameters. When data from all sources (EMS, transferring hospital and primary hospital) were included, the rule performed with a sensitivity of 98% 95% CI (96, 99%) and specificity of 26% 95% CI (23, 29%) for cervical spine injury. The sensitivity for identifying cervical spine injury requiring neurosurgical intervention using all sources of data was 98%, 95% CI (95, 99%). Because this is a case-control study, predictive values cannot be calculated. The author states the application of the rule could results in a 25% reduction in the use of imaging.

PECARN: PEDIATRIC CERVICAL SPINE RULE*		
PARAMETER*	TYPE	ADJUSTED ODDS RATIO (95% CI)
Predisposing condition	History	15.6 (2.9-78.0)
Diving	Mechanism	73 (9.6-555.6)
High risk motor vehicle collision	Mechanism	2.5 (1.8-3.6)
Complaint of neck pain	Symptom	3.2 (2.3-4.4)
Focal neurologic findings	Sign	8.3 (5.6-12.2)
Altered mental status	Sign	3.0 (2.1-4.3)
Substantial torso injury	Sign	1.9 (1.1-3.4)
Torticollis	Sign	1.8 (1.1-2.9)
*See appendix for parameter definitions		

APPLICABILITY: Some factors such as “substantial injury to the torso” are open to interpretation. Interrater reliability of the parameters in the rule could not be determined retrospectively. Only 27 patients less than two years of age were included possible limiting applicability to this age group. A separate rule for this group would have been beneficial to account for age dependent differences in cervical spine anatomy and injury patterns. Finally, this is a level 4 clinical decision rule that requires further validation before it can be applied clinically.

AUTHOR’S CONCLUSION: “This study represents a large investigation of cervical spine injury in children derived from primary source data. Although there were subtle differences between the conditional and unconditional models, the overall consistency between the models and the bootstrapping validation support the stability of the unconditional model. Application of this model as a decision rule within this sample of imaged children would have detected 98% of children with cervical spine injury and reduced exposure to spinal immobilization and ionizing radiation for the non– cervical spine injury children by more than 25%.

We identified 8 predictors of cervical spine injury in children after blunt trauma, including altered mental status, focal neurologic deficits, complaint of neck pain, torticollis, substantial torso injury, predisposing condition, diving, and high-risk motor vehicle crash. These factors should be highly considered in the development of a decision rule for the identification of children at negligible risk for cervical spine injury after blunt trauma, in whom immobilization and radiographic evaluation can be deferred.”

POTENTIAL IMPACT: This is a level 4 clinical decision rule that requires further validation before it can be applied clinically. Given the scarcity of pediatric cervical spine injuries (on average 8 per year per study center) and cervical spine injuries requiring neurosurgical intervention (on average 3 per year per study center) this may be difficult to achieve.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

APPENDIX: PARAMETER DEFINITIONS

PARAMETER DEFINITIONS	
Predisposing conditions	Down syndrome Klippel-Feil syndrome Achondrodysplasia Mucopolysaccaridosis Ehlers-Danlos syndrome Marfan syndrome Osteogenesis imperfecta Larsen syndrome Juvenile rheumatoid arthritis Juvenile ankylosing spondylitis Renal osteodystrophy Rickets History of CSI or cervical spine surgery
Diving	
High risk motor vehicle collision	Head on collision Rollover Ejected from vehicle Death in the same crash Speed > 55 mph
Complaint of neck pain	> 2 years
Focal neurologic findings	Paresthesias Loss of sensation Motor weakness Other focal neurologic findings
Altered mental status	GCS <15 AVPU < A (Alert, Voice, Pain, Unresponsive) Other findings suggestive of AMS
Substantial torso injury	Thorax including clavicles, abdomen, flanks, back, pelvis (e.g. rib fractures, visceral or solid organ injuries, pelvic fracture)
Torticollis	Torticollis, limited range of motion or difficultly moving the neck noted in Hx or PE

CERVICAL SPINE INJURY:
DECISION RULE RE-DERIVATION (PECARN)

In children less than 18 years of age who sustain blunt trauma are clinical signs and symptoms accurate in identifying those at low risk for cervical spine injury who could potentially forgo cervical spine imaging?

Michael Mojica, MD
July 2019

Leonard JC, Browne LR, Ahmad FA, Schwartz H, Wallendorf M, Leonard JR, Lerner EB, Kuppermann N.

CERVICAL SPINE INJURY RISK FACTORS IN CHILDREN WITH BLUNT TRAUMA.

Pediatrics. 2019 Jul;144(1).
PubMed ID: 31221898

STUDY DEFINITIONS	
POPULATION	Inclusion: < 18 years with blunt trauma Transported from the scene by EMS Present to the ED either directly via EMS or in transfer Underwent a trauma evaluation with or without cervical spine imaging Exclusion: Penetrating trauma Legal guardian with a significant English language barrier Transferred from the study site for definite care Setting: n=3 Level I trauma Children's Hospitals (U.S.), 3/2014-11/2016
RULE PARAMETERS	Factors with biologic or anatomic plausibility and good inter-rater reliability. Included: Mechanism of injury/injury biomechanics variables and patient history, signs and symptoms variables (See Appendix: Candidate variables)
REFERENCE STANDARD	Cervical Spine Injury: Occiput to C7 Vertebral fracture Ligamentous injury (including ligaments attached to T1) Intraspinal hemorrhage Spinal cord injury: MRI or spinal cord injury without radiographic abnormality ED imaging performed: Review of c-spine imaging reports and spine surgeon consultation notes if applicable No ED imaging performed: Medical record review at 28 days for subsequent imaging. If no imaging obtained then phone follow up at 21-28 days after ED visit
OUTCOME	Rule characteristics, potential reduction in XRAY utilization
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. An extensive list of candidate factors with biologic or anatomic plausibility and good inter-rater reliability were included in the derivation process (See Appendix: Candidate variables).
Were all important predictors present in significant proportion of the study population?	Unclear. The proportion of patients with the significant predictors was not presented. The others only note that predisposing conditions occurred in < 1 % of patients.
Were the outcome event and predictors clearly defined?	Yes. The outcome of cervical spine injury was clearly defined as an injury from the occiput to C7 (including ligamentous attachments to T1) involving the vertebra, ligaments, extraspinal space (hemorrhage) and spinal cord.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Yes. Data was collected prior to the results of imaging. For transfer patients, data was collected prior to imaging interpretation by the radiologist at the study institution but clinicians may have been aware of imaging results from the transferring institution. 42% (31/74) of those with cervical spine injury were transfers. However, when a subgroup analysis that excluded transfer patients was conducted, the test characteristics for both models remained similar.
Was the sample size adequate (including an adequate number of outcome events)?	In general, a sample size of 10 outcomes per variable in the model is considered adequate for logistic regression. 74 patients with cervical spine injury were included. 9 variables were included in the PECARN model (6 were statistically significant). 7 variables were included in de novo model.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SENSITIVITY AND PREDICTIVE VALUE OF A NEGATIVE RULE WITH 95% CONFIDENCE INTERVALS)
HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SPECIFICITY AND PREDICTIVE VALUE OF A POSITIVE RULE WITH 95% CONFIDENCE INTERVALS)

Cervical Spine Injury: 1.8% (74/4,091)
Mean age: 9.4 years (all patients), 10.7 years (patients with CSI)
Age < 8 years, 39.3% (1,608/4,091), CSI: 1.4% (23/1,608), 31.1% of those with CSI: (23/74)
Non-transfer patients: 76.7% (3,138/4,091), CSI: 1.4% (43/3,138)
Imaging obtained: 78.2%

INDEPENDENT PREDICTORS OF CSI: REGRESSION ANALYSIS

PREDICTOR	PECARN MODEL[1]	DE NOVO MODEL[1]
Mechanism: High Risk MVC	1.58 (0.63, 3.97)	
Mechanism: Diving	17.60 (5.60, 55.32)	9.16 (2.41, 34.83)
Mechanism: Axial Load		2.51 (1.22, 5.16)
History: Predisposing Condition	2.02 (0.27, 15.10)	
History: Neck Pain[2]	1.65 (1.04, 2.62)	2.87 (1.50, 5.48
History: Inability to Move Neck[2]	3.77 (2.00, 7.12)	3.51 (1.72, 7.17)
Exam: Altered Mental Status	5.67 (3.54, 9.09)	2.90 (1.37, 6.12)
Exam: Intubated		10.71 (4.43, 25.91)
Exam: Limited Neck Range of Motion	1.85 (0.88, 3.90)	
Exam: Substantial Torso Injury	2.61 (1.24, 5.53)	
Exam: Respiratory Distress		5.84 (1.56, 21.88)
Exam: Focal Neurologic Deficits	2.62 (1.04, 6.63)	

GREEN = Statistically Significant, RED = Not Statistically Significant
1. Adjusted Odds Ratio (95% Confidence Interval)
2. Neck pain and inability to move neck were assessed separately. These were combined as Torticollis in the derivation of the original PECARN case-control study

TEST CHARACTERISTICS

PECARN RULE		CSI		
		Yes	No	
≥ 1 Factor[1]	Yes	67	2,186	2,253
	No	7	1,831	1,838
		74	4,017	4,091
Sensitivity		90.54% (83.87, 97.21%)		
Specificity		45.58% (44.04, 47.12%)		
PV (+) Test		2.97% (2.27, 3.68%)		
PV (-) Test		99.62% (99.34, 99.90%)		
LR (+) Test		1.66 (1.54, 1.80)		
LR (-) Test		0.21 (0.10, 0.42)		

DE NOVO RULE		CSI		
		Yes	No	
≥ 1 Factor	Yes	68	1,998	2,066
	No	6	2,019	2,025
		74	4,017	4,091
Sensitivity		91.88% (85.7, 98.11%)		
Specificity		50.26% (48.72, 51.81%)		
PV (+) Test		3.29% (2.52. 4.06%)		
PV (-) Test		99.71% (99.47, 99.94%)		
LR (+) Test		1.85 (1.71, 1.99)		
LR (-) Test		0.16 (0.07, 0.35)		

1. Any of the 9 factors in the PECARN rule including the 3 that were not statistically significant

SUBGROUP ANALYSIS (WITH/WITHOUT TRANSFER PATIENTS)

		SENSITIVITY	SPECIFICITY
PECARN Model	All Patients	90.5% (83.9, 97.2%)	45.6% (44.0, 47.1%)
	Transfers Excluded	93.0% (85.4, 100%)	42.1% (40.3, 43.8%)
De Novo Model	All Patients	91.9% (85.7, 98.1%)	50.26% (48.7, 51.8%)
	Transfers Excluded	95.3% (89.1, 100%)	45.9% (44.1, 47.7%)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

Utilizing the PECARN rule, 44.9% (1,838/4,091) of patients did not have any risk factors and could potentially forgo imaging. Alternatively, 55.1% would have imaging if those with at least 1 factor underwent imaging.

Utilizing the De Novo rule 49.4% (2,024/4,091) of patients did not have any risk factors and could potentially forgo imaging. Alternatively, 51.6% would have imaging if those with at least 1 factor underwent imaging.

The potential decrease in imaging would depend on the baseline rate of imaging. The authors extrapolated a decrease in the rate of imaging from a baseline rate of 78.2%. Imaging wound potential be reduced by 22.1% (78.2% - 55.1%) for the PECARN rule and by 26.6% (78.2% - 51.6%) for the De Novo rule.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

Interval validation of the rule was not presented. The original PECARN derivation study had a higher sensitivity of 98%, 95% CI (96, 99%) and a lower specificity of 26%, 95% CI (23, 29%).

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (See Appendix)	❑ I ❑ II ❑ III ■ IV The de novo rule is level IV rule. The PECARN rule is also a level IV rule (a re-derivation with different predictors). A level IV rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. A level IV rule requires further validation before it can be applied clinically.
Does the rule make clinical sense?	Yes. The factors in both of the rules assess factors that are associated with cervical spine injury. However, a distracting injury which is a factor in the NEXUS criteria was not assessed as a candidate variable though it is the most subjective of the NEXUS criteria.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. The authors included factors with biologic or anatomic plausibility and good inter-rater reliability. The kappa statistics for the significant predictors were not presented.
Is the rule applicable to the patients in my practice?	Yes. We evaluate pediatric trauma patients with a potential for cervical spine injury. However, motor vehicle collision was the most common mechanism of injury in the study and pedestrians struck by motor vehicles is a more common mechanism in NYC. It is unclear if these mechanisms result in different patterns of injury.
Will the rule results change my management strategy?	Unlikely. These are the parameters that we currently use to assess the risk of c-spine injury. I would wait for the follow up study in the entire PECARN network to validate the two models. Only 74 patients with c-spine injury were included in the analysis (n=23 in those less than 8 years of age).
What are the benefits of applying the rule to my patients?	The primary benefit of using either of the decision rules is a reduction in imaging. Pediatric plain films are often difficult to obtain and interpret. CT scan is associated with radiation exposure. The authors extrapolated a decrease in the rate of imaging from a baseline rate of 78.2%. Imaging wound potential be reduced by 22.1% (78.2% - 55.1%) for the PECARN rule and by 26.6% (78.2% - 51.6%) for the De Novo rule.
What are the risks of applying the rule to my patients?	The primary risk of applying either of the decision rules is in missing patients with a cervical spine injury. The PECARN rule missed 9.5% (7/74) of those with cervical spine injury. The de novo rule missed 8.1% (6/74) of those with cervical spine injury. 6 of the patients missed did not require surgical intervention. Treatment of the 7th patient is unknown. 1 missed patient required a brace and another required a hard, cervical collar (Table 5).

CLINICAL BOTTOM LINE

BACKGROUND: Pediatric cervical spine injuries are rare (< 1% after blunt trauma). Decision rules to identify risk of cervical spine injury in adults have been developed (NEXUS criteria, Canadian C- spine rule). A pediatric rule was developed as a subset of the Nexus study. (Vicellio, Pediatrics 2001, PubMed ID: 11483830). The pediatric NEXUS included only 30 patients with cervical spine injuries. While the sensitivity of the rule was 100%, the lower limit of the 95% confidence interval was 88% due to the small sample size.

The PECARN group previously conducted a case-control study to derive a pediatric cervical spine clinical decision rule (Leonard, Ann Emerg Med. 2011, PubMed ID: 21035905). The study identified 8 predictors of pediatric cervical spine injury. These included 1 history parameter (predisposing conditions), 2 mechanism of injury parameters (diving, high risk motor vehicle collision), 1 symptom parameter (complaint of neck pain) and 4 physical examination parameters (focal neurologic deficit, altered mental status, substantial torso injury, torticollis). The rule performed with a sensitivity of 98% 95% CI (96, 99%) and specificity of 26% 95% CI (23, 29%) for cervical spine injury. The sensitivity for identifying cervical spine injury requiring neurosurgical intervention using all sources of data was 98%, 95% CI (95, 99%). To date, the rule has not been validated.

CLINICAL QUESTION: In children less than 18 years of age who sustain blunt trauma are clinical signs and symptoms accurate in those at low risk of cervical spine injury who could potentially forgo cervical spine imaging?

DESIGN/RISK OF BIAS: This was a well-designed prospective cohort study conducted at 4 children's hospitals that are level I trauma centers. Patients less than 18 years with blunt trauma who were transported from the scene by emergency medical services to the ED either directly or in transfer from another institution and who underwent a trauma evaluation with or without cervical spine imaging were included. Patients with penetrating trauma, a legal guardian with a significant English language barrier and those who were transferred from the study site for definite care were excluded.

Candidate predictors were those with biologic or anatomic plausibility and good inter-rater reliability. These included mechanism of injury/injury biomechanics variables and patient history, signs and symptoms variables (See Appendix: Candidate Variable). The outcome of cervical spine injury was clearly defined as an injury from the occiput to C7 (including ligamentous attachments to T1) involving the vertebra, ligaments, extraspinal space (hemorrhage) and spinal cord. The outcome was assessed by review of c-spine imaging reports and spine surgeon consultation notes if applicable for those that had imaging. The outcome was assessed by medical record review at 28 days to determine is subsequent imaging was obtained. If no subsequent imaging was obtained then phone follow-up occurred at 21-28 days after ED visit.

It is somewhat unusual to include transfer patients as knowledge of the reason for transfer including imaging results may bias interpretation of the predictor variables. For transfer patients, data was collected prior to imaging interpretation by the radiologist at the study institution but clinicians may have been aware of imaging results at the transferring institution. 42% (31/74) of those with cervical spine injury were transfers. However, when a subgroup analysis that excluded transfer was conducted, the test characteristics for both models remained similar. In addition, the proportion of patients with the significant predictors was not presented.

PRIMARY RESULTS: Cervical spine injury occurred in 1.8% (74/4,091). 39.3% of the patients were less than 8 years of age. These patients had a cervical spine injury rate of 1.4% (23/1,608). 23.3% of the patients were transferred and imaging was obtained in 78.2% of patients.

7 independent predictors of cervical spine injury were identified in the de novo model. In the PECARN model 3 of the 9 predictors identified in the derivation were not statistically significantly associated with cervical spine injury in the regression analysis. These were high risk motor vehicle collision, predisposing medical condition and limited neck range of motion on examination. Four factors were common to both rules. These include: a mechanism of diving, a history of neck pain, a history of inability to move the neck and physical examination consistent with altered mental status. Of note, neck pain and inability to move neck were assessed separately (these were combined in the original PECARN derivation as torticollis).

INDEPENDENT PREDICTORS OF CSI: REGRESSION ANALYSIS		
PREDICTOR	PECARN MODEL[1]	DE NOVO MODEL[1]
Mechanism: High Risk MVC	1.58 (0.63, 3.97)	
Mechanism: Diving	17.60 (5.60, 55.32)	9.16 (2.41, 34.83)
Mechanism: Axial Load		2.51 (1.22, 5.16)
History: Predisposing Condition	2.02 (0.27, 15.10)	
History: Neck Pain[2]	1.65 (1.04, 2.62)	2.87 (1.50, 5.48
History: Inability to Move Neck[2]	3.77 (2.00, 7.12)	3.51 (1.72, 7.17)
Exam: Altered Mental Status	5.67 (3.54, 9.09)	2.90 (1.37, 6.12)
Exam: Intubated		10.71 (4.43, 25.91)
Exam: Limited Neck Range of Motion	1.85 (0.88, 3.90)	
Exam: Substantial Torso Injury	2.61 (1.24, 5.53)	
Exam: Respiratory Distress		5.84 (1.56, 21.88)
Exam: Focal Neurologic Deficits	2.62 (1.04, 6.63)	

GREEN = Statistically Significant, RED = Not Statistically Significant
1. Adjusted Odds Ratio (95% Confidence Interval)
2. Neck pain and inability to move neck were assessed separately. These were combined in the original PECARN derivation as Torticollis

Test characteristics were slightly better for the de novo rule than for the PECARN rule. However, a statistical comparison of the test characteristics was not presented. Test characteristics did not differ appreciably in a subgroup analysis that excluded transfer patients.

The de novo rule divided a group with 1.8% cervical spine injury into a low risk group if there were no risk factors (1-PV(-) = 0.3%) and a high risk group (PV(+) = 3.3% if at least 1 factor was present.

The PECARN rule divided a group with 1.8% cervical spine injury into a low risk group if there were no risk factors (1-PV(-) = 0.3%) and a high risk group (PV(+) = 3.0% if at least 1 factor was present.

The original PECARN derivation study had a higher sensitivity of 98%, 95% CI (96, 99%) but a lower specificity of 26%, 95% CI (23, 29%).

TEST CHARACTERISTICS									
PECARN RULE		CSI			DE NOVO RULE		CSI		
		Yes	No				Yes	No	
≥ 1 Factor[1]	Yes	67	2,186	2,253	≥ 1 Factor	Yes	68	1,998	2,066
	No	7	1,831	1,838		No	6	2,019	2,025
		74	4,017	4,091			74	4,017	4,091
Sensitivity		90.54% (83.87, 97.21%)			Sensitivity		91.88% (85.7, 98.11%)		
Specificity		45.58% (44.04, 47.12%)			Specificity		50.26% (48.72, 51.81%)		
PV (+) Test		2.97% (2.27, 3.68%)			PV (+) Test		3.29% (2.52. 4.06%)		
PV (-) Test		99.62% (99.34, 99.90%)			PV (-) Test		99.71% (99.47, 99.94%)		
LR (+) Test		1.66 (1.54, 1.80)			LR (+) Test		1.85 (1.71, 1.99)		
LR (-) Test		0.21 (0.10, 0.42)			LR (-) Test		0.16 (0.07, 0.35)		
1. Any of the 9 factors in the PECARN rule including the 3 that were not statistically significant									

APPLICABILITY: The inclusion of transfer patients in the study likely makes the study's results generalizable to patients meeting the study's inclusion and exclusion criteria.

The de novo rule is level IV rule. The PECARN rule is also a level IV rule (a re-derivation with different predictors). A level IV rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. A level IV rule requires further validation before it can be applied clinically.

AUTHOR'S CONCLUSION: "In this prospective cohort of children with blunt trauma, we confirmed that there are risk factors with good test accuracy in identifying cervical spine injury. We also demonstrated that incorporating these risk factors into a clinical prediction rule has the potential to substantially reduce cervical spine imaging during trauma evaluation of children. A future, adequately powered prospective observational study aimed at using these risk factors to construct a definitive pediatric cervical spine injury prediction rule is warranted."

POTENTIAL IMPACT: This is a pilot study in one of the PECARN network nodes that will be further investigated in the larger PECARN network. The study demonstrated the use of the rule could potentially decrease imaging usage by 20-25% at the expense of rarely missing patients with cervical spine injury ((8-10% of those with CSI were not identified by the rules). None of the missed patients required a surgical intervention. The small number of patients with c-spine injury (n=74) (n=23 in those less than 8 years of age) results in wide confidence intervals.

The authors conclude that further study is required before implementation of either rule. I would recommend waiting for the follow-up study in the entire PECARN network to validate the two models before changing clinical practice.

APPENDIX: CANDIDATE VARIABLES

CANDIDATE VARIABLES
MECHANISM OF INJURY AND INJURY BIOMECHANICS
High risk motor vehicle collision
Compartment intrusion: Roof > 12 inches at passenger site or > 18 inches at any site
Partial of complete ejection from the vehicle
Death of a passenger in the same compartment
Vehicle telemetry consistent with high-risk crashes
Diving, axial load of clotheslining
Force caused by a rope, cable or other similar exerting traction on neck while body moving forward
PATIENT HISTORY VARIABLES
Predisposing conditions
Loss of consciousness
Neck pain
Inability to move neck
Paresthesias
Numbness
Weakness
PHYSICAL EXAMINATION FINDINGS
Altered mental status
Intubation
Signs of substantial head injury other than altered mental status
Signs of basilar skull fracture
Posterior midline neck tenderness to palpation
Limited range of neck motion
Substantial* torso injury
Substantial* thorax injury
Substantial* abdominal injury
Substantial* pelvic injury
Decreased oxygen saturation
Thoracic spine tenderness
Lumbar spine tenderness
Sacral spine tenderness
Focal neurologic deficits: Paresthesia, decreased sensation, weakness
*Substantial injury: Life threatening and warranting surgical intervention OR warranting inpatient observation

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

CERVICAL SPINE INJURY:
PEDIATRIC NEXUS CRITERIA VALIDATION

In pediatric blunt trauma patients, less than 18 years of age, are the National XRAY Utilization Study (NEXUS) criteria accurate in identifying those with and without a cervical spine injury?

Michael Mojica, M.D.
January 2017

Viccellio P, Simon H, Pressman BD, Shah MN, Mower WR, Hoffman JR; NEXUS Group.

A PROSPECTIVE MULTICENTER STUDY OF CERVICAL SPINE INJURY IN CHILDREN

Pediatrics. 2001 Aug;108(2): E20.
PubMed: 11483830

STUDY DEFINITIONS	
POPULATION	Inclusion: Blunt trauma patients, < 18 years, cervical spine XRAYS ordered Exclusion: Penetrating trauma, C-spine XRAYS for a non-trauma indication Setting: 21 centers (academic/community, public/private, with/without residency, small/large, varying levels of trauma certification). The enrollment period was not specified.
INTERVENTION	NEXUS Cervical spine rule criteria: Absent, Present, Unable to assess 1. No midline cervical tenderness 2. No focal neurologic deficit 3. Normal alertness 4. No intoxication 5. No painful, distracting injury Site investigators underwent 1 hour of training in the implementation of the rule and then trained site clinicians either formally or informally
CONTROL	C-spine XRAY: Cross table lateral, anterior-posterior, open-mouth (odontoid). CT or MRI could have been ordered if plain XRAYS were impractical/ impossible
OUTCOME	Rule Characteristics Potential reduction in XRAY utilization
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were the patients chosen in an unbiased fashion and do they represent a wide spectrum of severity of disease?	Unclear. All patients with blunt trauma for which C-spine XRAYS were ordered were included. This was a multicenter study and indications for XRAY utilization in blunt trauma were not pre-defined by the study. Patient characteristics other than an age range and gender are not presented.
Was there a blinded assessment of the criterion standard for all patients?	Yes. Radiologists interpreting the XRAY were masked to the rule criteria. Final interpretation of the XRAY was by a designated radiologist. If the radiology report was ambiguous the designated radiologist reviewed both the report and the XRAY. It is unclear if pediatric radiologists interpreted the XRAYs. There are many anatomic variants that lead to different patterns of injury than adults and may mimic adult injuries.
Was there an explicit and accurate interpretation of the predictor variables and the actual rule without knowledge of the outcome?	Yes. Clinicians completed the assessment of the rule criteria before the results of XRAYS were available. The rule criteria were not explicitly defined. This was intentional. The authors state that this was done because “the criteria could not be precisely defined in a clinically meaningful way” and extensive definitions would impede usability of the rule. Examples of possible interpretations were reviewed during training and were available on a site computer.
Was there 100% follow up of those enrolled?	Unclear. All patients were followed until XRAY results were available. No effort was made to contact patients after discharge. Neurosurgical records were reviewed for 3 months to identify missed injuries

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

N = 3,065
Cervical spine injury: 30/365 = 0.98%

CERVICAL SPINE INJURY (CSI) BY AGE

	N	CSI
< 2 years (lack of verbal ability)	88	0
2-8 years (immature cervical spine)	817	4
9-17 years (mature cervical spine)	2,160	26
TOTAL	3,065	30

		CERVICAL SPINE INJURY		
		YES	NO	
NEXUS RULE	POSITIVE	30	2,432	2,462
	NEGATIVE	0	603	603
		30	3,035	3,065

Prevalence: 30/3,065 = 0.98%
Sensitivity: 30/30 = 100%, 95% CI (87.8, 100%)
Predictive Value (-) Rule: 603/603 = 100% (99.2, 100%)
Specificity: 603/3,065 = 19.9% (18,5, 21.3%)
Predictive Value (+) Rule: 30/2,462 = 1.2% (0.8%, 1.8%)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

80.3% (2,462/3,065) had a positive rule and would have an XRAY performed. Since 100% of the patients in the study had XRAYs, use of the rule would have potentially decreased the rate of XRAY by 19.7% (100% - 80.3%)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see appendix)	☐ I ■ II ☐ III ☐ IV This is level II clinical decision rule. A level II rule has been validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. An impact analysis has not been completed. A level II rule can be used rule in a wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve.
Does the rule make clinical sense?	Yes. The rule makes clinical sense. The rule parameters are those that are typically used to assess for the possibility for cervical spine injury. An exception is that a parameter for mechanism of injury was not included.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. The authors provide a range of inter-rater reliability (kappa statistic) of 0.58-0.86 for the rule criteria but do not report inter-rater reliability for individual criteria. Inter-rater reliability for the rule as a whole (rule positive vs rule negative) was good (kappa 0.73). The kappa statistics for the rule parameters or the rule as a whole are reported for the data set including both adults and children and are not provided separately for pediatric patients.
Is the rule applicable to the patients in my practice?	This rule included patients of all ages. There were 3,065 patients included less than 18 years of age. Of these only 817 patients were less than or equal to 8 years of age and 88 less than 2 years of age. Only 4 cervical spine injuries occurred in those 2-9 years or age and none less than 2 years.
Will the rule results change my management strategy?	Yes. The rule is used currently in adolescent patients to assess for the need for cervical spine XRAY?
What are the benefits of applying the rule to my patients?	The potential benefit of the use of the rule is a reduction in those requiring XRAYS. In the study population 19.6% of the patients were considered negative and potentially could have avoided XRAY. An impact analysis of the rule is necessary to assess that actual reduction in XRAY utilization.
What are the risks of applying the rule to my patients?	The greatest potential risk is in missing a patient with a cervical spine injury who could then be at risk of a spinal cord injury. While both the sensitivity and negative predictive value of the rule are 100%, the lower limit of the 95% confidence interval include the possibility of missing patients with a cervical spine injury.

CLINICAL BOTTOM LINE

BACKGROUND: The rate of pediatric cervical spine injury in blunt trauma patients is low (1-2%). Missing a patient with a cervical spine injury can have devastating effects. Anatomic differences in the pediatric cervical spine predispose children to a different range of injuries and adult cervical spine clearance algorithms may not be applicable. A clinical decision rule that could identify clinical characteristics of those at low risk for a cervical spine injury could potentially decrease cervical spine XRAY or CT utilization in pediatric blunt trauma patients.

CLINICAL QUESTION: In pediatric blunt trauma patients less than 18 years of age are the National XRAY Utilization Study (NEXUS) criteria accurate in identifying those with and without a cervical spine injury?

DESIGN/RISK OF BIAS: This was a well-designed prospective cohort of patients with blunt trauma for which cervical spine XRAY's were ordered. This study is a sub-analysis of pediatric patients form the validation of the NEXUS criteria (Hoffman, NEJM 2000, PubMed: 10891516). The study was performed to assess the validity of the NEXUS criteria and included 3,065 patients. There was little description of the patient population other than an age categories. The indication for XRAY were not specified. No effort was made to contact patients after discharge though neurosurgical records were reviewed for 3 months to identify missed injuries. It is unclear if pediatric radiologist interpreted the XRAYs. There are many anatomic variants that lead to different patterns of injury than adults and that may mimic adult injuries. The cervical spine injuries were not classified as in the main NEXUS study as clinically significant or not.

PRIMARY RESULTS: 0.98% of patients had cervical spine injury. The rule was accurate in identifying those with any cervical spine injury (Sensitivity: 100%, 95% CI (87.8, 100%), Predictive Value of a Negative Rule: 100%, 95% CI (99.2, 100%). The rule was less accurate in identifying those without a cervical spine injury (Specificity: 19.9%, 955 CI (18,5, 21.3%)

The rule stratified patients with a baseline risk of cervical spine injury of 0.98% into a low-risk group (CSI rate 0.0%) if the rule was negative and a high-risk group (CSI rate = 1.2%) if the rule was positive.

NEXUS CERVICAL SPINE RULE CRITERIA*		
NO	N	Neurologic deficit (focal)
	S	Spinal Tenderness (midline)
	A	Altered Mental Status
	I	Intoxication
	D	Distracting injury (painful)
*Rule criteria evaluated as: Absent, Present or Unable to assess If unable to assess the criteria is considered present and XRAYS are indicated		

80.3% of patients had a positive rule and would have an XRAY performed. Since 100% of the patients in the study had XRAYs, use of the rule would have potentially decreased the XRAY rate by 19%.

APPLICABILITY: The low number of patients less than 8 years of age (905) and cervical spine injuries (n=4) makes application of the rule to this age group questionable. The use of 21 hospitals with varying characteristics likely make the study's results generalizable to the majority of patients with blunt trauma in which a cervical spine injury is suspected. The authors provide a range of inter-rater reliability (kappa statistic) of 0.58-0.86 for the rule criteria but do not report inter-rater reliability for individual criteria. Inter-rater reliability for the rule as a whole (rule positive vs rule negative) was good (kappa 0.73). The kappa statistics for the rule parameters or the rule as a whole are reported for the data set including both adults and children and are not provided separately for pediatric patients.

The rule criteria were not explicitly defined. This was intentional. The authors state that this was done because "the criteria could not be precisely defined in a clinically meaningful way" and extensive definitions would impede usability of the rule.

This is level II clinical decision rule. A level II rule has been validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. An impact analysis has not been completed. A level II rule can be used rule in a wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve.

AUTHOR'S CONCLUSION: "This prospective observational study, the largest (and only prospective) study ever done regarding pediatric CSI, provides a great deal of information about this entity and strongly suggests that children who meet all of the NEXUS low-risk criteria generally do not need to undergo cervical spine imaging. Given the small number of children with CSI in this series, we urge caution in applying the decision instrument to individual patients, particularly in the youngest age groups, in which the number of study participants was relatively small. Nevertheless, our data suggest that CSI is at most extremely rare among children who are defined as low risk by the decision instrument, concordant with both the absence of any report of occult fracture in the pediatric literature and the overall results among all 34,069 NEXUS participants. We believe that this strongly supports the safety and utility of the NEXUS criteria in children, application of which could reduce cervical spine imaging in children by approximately 20%, limit the time in which children are forced to remain immobilized, and decrease their exposure to radiation. Finally, utilization of the NEXUS decision instrument should lead to a substantial reduction in health care costs through avoidance of unnecessary radiographs."

POTENTIAL IMPACT: This was a well-designed study that has the potential to decreased XRAY utilization. An impact analyses is required to determine that actual rate of imaging reduction. The rule should be used with caution if at all in patients less than 8 years of age. The potential for rarely missing a patient with a clinically significant cervical spine injury should be considered and factors other than the rule criteria (such as a high-risk mechanism of injury e.g. diving) may also contribute to the decision to obtain cervical spine XRAYs.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

CERVICAL SPINE INJURY: TODDLER DECISION RULE DERIVATION

In children less than three years of age admitted for blunt trauma, do clinical predictors that do not rely on patient cooperation adequately identify those with and without cervical spine injury?

Kelly Cleary, M.D., Michael Tunik, M.D.
November 2009

Pieretti-Vanmarcke R, Velmahos GC, Nance ML, Islam S, Falcone RA Jr, Wales PW, Brown RL, Gaines BA, McKenna C, Moore FO, Goslar PW, Inaba K, Barmparas G, Scaife ER, Metzger RR, Brockmeyer DL, Upperman JS, Estrada J, Lanning DA, Rasmussen SK, Danielson PD, Hirsh MP, Consani HF, Stylianos S, Pineda C, Norwood SH, Bruch SW, Drongowski R, Barraco RD, Pasquale MD, Hussain F, Hirsch EF, McNeely PD, Fallat ME, Foley DS, Iocono JA, Bennett HM, Waxman K, Kam K, Bakhos L, Petrovick L, Chang Y, Masiakos PT.

CLINICAL CLEARANCE OF THE CERVICAL SPINE IN BLUNT TRAUMA PATIENTS YOUNGER THAN 3 YEARS: A MULTI-CENTER STUDY OF THE AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA

J Trauma. 2009 Sep;67(3):543-9.
PubMed ID: 19741398

STUDY DEFINITIONS	
POPULATION	Inclusion: < 3 years, blunt trauma, site part of a trauma registry Exclusion: > 3 years Setting: 22 centers (United States (19), Canada (2), Brazil (1)). Pediatric level I (15), Adult level I (6), Adult level II (1). 1/1995–1/2005
RULE PARAMETERS	Trauma registry data: Age, gender, mechanism of injury (motor vehicle crash fall, assault, other), Injury Severity Score, Abbreviated Injury Score (head and neck, face), paralysis, Glasgow Coma Score (GCS), total and sub-scores (eye, verbal motor), imaging, mortality. Cervical Spine Injury Patients: Medical records reviewed: exact circumstances of injury, presentation, physical findings on arrival, diagnostic tests, type of injury (ligamentous or fracture), treatment
REFERENCE	Cervical spine osseous or ligamentous injury on CT, XRAY, or MRI
OUTCOME	Decision rule characteristics Reduction in imaging utilization
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	No. Though the intent of the study was to only include factors that did not rely on patient cooperation.
Were all important predictors present in significant proportion of the study population?	Unclear. The proportion of patients with each of the 4 identified predictors was not presented.
Were the outcome event and predictors clearly defined?	Yes. The outcome of cervical spine injury was clearly defined as any osseous or ligamentous injury to the cervical spine seen on MRI, CT, or radiograph. The authors did not distinguish between all cervical spine injuries (CSI) and clinically significant CSI. Those who did not undergo imaging were assumed to be without CSI and were not followed up. Imaging modality was at the discretion of the examining physician: clinical clearance, XRAY, CT, MRI. The rule predictors: motor vehicle collision and age are objective though the severity of a motor vehicle collision is subjective. It is unclear, what the reproducibility of Glasgow Coma Scale is in this age group.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Unclear. This was a retrospective database collection; the authors do not comment on blinding.
Was the sample size adequate (including an adequate number of outcome events)?	Yes. Total sample size was > 12,000 patients. In general, for logistic regression it is recommended to have approximately 10 outcomes for each of the rule predictors. The final rule had 4 predictors and the study included 80 patients with cervical spine injury

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

N = 12,537 patients
83 confirmed CSI (0.66%)
Imaging: XRAY: (32.3%), CT: (30.6%), MRI: (3.8%).
Sensitivity: 94%, 95% CI (86.7, 97.4%)
Predictive Value (-) Rule: 99.9%, 95% CI (99.9, 100%)

CERVICAL SPINE INJURY WEIGHTED SCORE

RULE PARAMETER	POINTS	ADJUSTED OR (95% CI)
Glasgow Coma Scale < 14	3	12.5 (5.0, 31.6)
Glasgow Come Scale (Eye) = 1	2	5.1 (2.8, 9.0)
Motor vehicle collision	2	6.9 (3.4, 14.2)
Age 2-3 years (24-36 months)	1	2.2 (1.2, 4.0)

COMBINED DERIVATION & VALIDATION SETS

		CERVICAL SPINE INJURY		
		YES	NO	
SCORE	≥ 2	78	3,748	3,826
	< 2	5	8,702	8,707
		83	12,450	12,533

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

Specificity: 69.9%, 95% CI (69.1, 70.7%%)
Predictive Value (+) Rule: 2%, 95% CI (1.6%, 2.5%)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

Imaging only patients with a rule score of ≥ 2 would results in an imaging rate of 30% (3,826/12,533). Approximately 66% of the study population underwent imaging though there was great variability by site. Application of the rule has the potential to decrease imaging utilization by approximately 36% (66% without the rule – 30% with the rule = 36%).

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

The prediction rule was validated using 1/3 of data set
Sensitivity (Validation set): 93.3%. (76, 98.8%)
Specificity (Validation set): 70.4%. (69, 71%)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (See appendix)	☐ I ☐ II ☐ III ■ IV This is a level IV clinical decision rule. Level IV rule have been derived only or validated only in split samples, large retrospective databases or by statistical methods. Level IV rules require further validation before it can be applied clinically
Does the rule make clinical sense?	Yes. The rule makes sense.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Yes. The rule parameters (Glasgow Coma Scale, age and motor vehicle collision) are easy to determine and are objective. Because this was a retrospective study, inter-relator reliability on the rule predictors was not possible for Glasgow Coma Scale.
Is the rule applicable to the patients in my practice?	Patients in the trauma registry (and seen a major trauma centers) are often those with higher acuity. The rule may not apply to other settings.
Will the rule results change my management strategy?	No. Not at this time. The rule requires further validation
What are the benefits of applying the rule to my patients?	The primary benefit of applying this rule is a reduction in the need for imaging. Approximately 2/3 of the study population underwent imaging. A decreased in the imaging rate may also decreased the need for sedation and facilitate the examination of a happier child when the collar is removed. A rule score < 2 would have resulted in approximately 30% undergoing imaging. Further validation and an impact analysis are required.
What are the risks of applying the rule to my patients?	The primary risk of applying the rule is missing a patient with a cervical spine injury. The low end of the CI for sensitivity in the derivation and validation groups were 83% and 76% respectively; indicating that as many as 24% could be missed using the rule. It is unclear if other clinical factors, such as a depressed mental status, or significant head trauma would have been alternative indications for cervical spine imaging in the 5 missed patients.

CLINICAL BOTTOM LINE

BACKGROUND: Clinical evaluation of the pediatric cervical spine is limited by patient cooperation. Clinical parameters such as spinal tenderness, altered mental status and distraction injury, which are part of the NEXUS criteria, are difficult to assess in the crying or agitated child.

CLINICAL QUESTION: In children less than three years of age admitted for blunt trauma do clinical predictors that do not rely on patient cooperation adequately predict cervical spine injury?

DESIGN/RISK OF BIAS: This study, using retrospective trauma registry data, attempts to identify clinical predictors of cervical spine injury (CSI) that do not rely on patient cooperation. The study aim was to identify children less than 3 years of age at low risk of CSI with the potential to limit imaging in this population. The study included 12,537 patients of which 83 (0.66%) had a confirmed CSI. Data collection was limited to the reliably of data available in the trauma registry. The data available did not allow at determination of whether a cervical spine injury was “stable” or ‘unstable” so that the clinical relevance of the injuries identified is unclear.

A number of validity concerns were identified in the study design. This was a retrospective cohort study with the potential bias’s inherent to that design such a recording bias. No follow-up was done to ensure that among those patients who were not imaged had a cervical spine injury that was identified subsequently. Almost ½ of eligible patients (10,000 out of 22,000) were not included due to missing data elements. No information regarding these patients, and the possible bias caused by excluding them are discussed by the authors.

PRIMARY RESULTS: The authors identified four independent predictors of cervical spine injury: GCS < 13, GCS(EYE) =1, Age 2-3 years, and a mechanism involving a motor vehicle collision. A weighted score of < 2 was considered low risk of cervical spine injury. The rule was fairly accurate in identifying those with a cervical spine injury (Sensitivity: 94%, 95% CI (86.7, 97.4%), Predictive Value (-) Rule: 99.9%, 95% CI (99.9, 100%). It was less accurate in identifying those without a cervical spine injury (Predictive Value (+) Rule: 2%, 95% CI (1.6%, 2.5%). The rule stratified a cohort with a 0.66% prevalence of cervical spine injury into a low risk group (Score < 2, 0.1% CSI) and a high-risk group (Score ≥ 2, 2% CSI).

There was great variability in the frequency of cervical spine imaging at a select group of participating trauma centers. Pediatric trauma centers utilized imaging less frequently. Imaging only patients with a rule score of ≥ 2 would results in an imaging rate of 30% (3,826/12,533). Approximately 66% of the study population underwent imaging though there was great variability by site. Application of the rule has the potential to decrease the imaging utilization by approximately 36% (66% without the rule – 30% with the rule). Specificity: 69.9% (69.1, 70.7%%)

CERVICAL SPINE INJURY WEIGHTED SCORE (< 3 YEARS)	POINTS
Glasgow Coma Scale < 14	3
Glasgow Come Scale (Eye) = 1	2
Motor vehicle collision	2
Age 2-3 years (24-36 months)	1

APPLICABILITY: There was limited information was provided on the study population. In addition, patients in the trauma registry are those with higher acuity (potential for referral bias). Therefore, the rule may not apply to patients presenting to other settings. Since the rule relies heavily on the Glasgow Coma Scale (5 of the 8 total points) it would be helpful to determine the inter-rater reliability of the total GCS and the GCS eye sub score in this age group.

This is a level IV clinical decision rule. Level IV rule have been derived only or validated only in split samples, large retrospective databases or by statistical methods. Level IV rules require further validation before it can be applied clinically.

AUTHOR'S CONCLUSION: "The common belief that is shared by many clinicians that the physical examination can be unreliable in a child younger than 3 years of age causes some to include routine imaging in the clinical decision rules for cervical spine clearance. We have demonstrated that clinical evaluation of these youngest trauma patients with suspected cervical spine injury in fact is quite effective in predicting, which subset of patients will benefit from cross-sectional imaging. Four simple clinical criteria used in concert with the physical examination can safely predict cervical spine injury in patients younger than 3 years. A WS of 0 or 1 offers a very high negative predictive value for cervical spine injury (99.9%), which is similar to what has been reported for imaging modalities when they are applied to this age group.

In this study, more than two thirds of children younger than 3 years who presented after blunt trauma would have had their cervical spines cleared using our scoring system and physical examination alone without being subjected to the risks of imaging studies. Although there is greater tendency for cervical spine injury to occur inpatients with higher scores, it is clear that even in this population, the incidence of cervical spine injury is very low. Therefore, cross-sectional imaging for patients with scores higher than 1 should be performed based on the individual assessment of the patient and the clinical judgment of the provider. To definitively demonstrate the effectiveness of the clinical decision rule (PEDSPINE) in this population (patients younger than 3 years of age), we would support a multicenter prospective randomized clinical trial."

POTENTIAL IMPACT: This is the largest study to date focusing on cervical spine injury in those less than 3 years of age. Despite the inclusion of 22 trauma centers over a 10-year period only 83 cervical spine injuries were included. The highlights the potential to reduce image utilization in this population. A decision rule based only on findings that are not dependent on patient cooperation would be very valuable. This study to the first step in deriving that rule but further validation is required. Further studies should focus on some of the validity and applicability issues what we reviewed.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

CONCUSSION:
RETURN TO PHYSICAL ACTIVITY

In children 5-18 years of age presenting to the emergency department after an acute injury and who meet concussion criteria is physical activity within 7 days of injury when compared to no physical activity within 7 days, associated with an increased risk of persistent post concussive symptoms at 28 days?

Michael Mojica, M.D.
July 2017

Grool AM, Aglipay M, Momoli F, Meehan WP 3rd, Freedman SB, Yeates KO, Gravel J, Gagnon I, Boutis K, Meeuwisse W, Barrowman N, Ledoux AA, Osmond MH, Zemek R; Pediatric Emergency Research Canada (PERC) Concussion Team.

ASSOCIATION BETWEEN EARLY PARTICIPATION IN PHYSICAL ACTIVITY FOLLOWING ACUTE CONCUSSION AND PERSISTENT POSTCONCUSSIVE SYMPTOMS IN CHILDREN AND ADOLESCENTS.

JAMA. 2016 Dec 20;316(23):2504-2514.
PubMed ID: 27997652

STUDY DEFINITIONS	
POPULATION	Inclusion: 5-18 years of age, acute head injury (within 48 hours), meeting concussion criteria from the Zurich Concussion Statement (2012) Exclusion: Glasgow Coma Score $\leq$ 15 Any abnormality on brain CT or MRI Neurosurgical intervention Intubation Intensive care unit admission Multisystem injury requiring admission Intoxication Absence of trauma Enrolled previously Insurmountable language barrier Inability to follow-up by phone or email Severe, preexisting neurologic condition limiting communication Setting: Children's Hospitals (9) in PERC (Pediatric Emergency Medicine Research Canada), 8/2013-6/2015
EXPOSURE	Exposure: Early physical activity* of any level within 7 days of enrollment 1. Light aerobic exercise: e.g. walking, swimming, stationary cycling 2. Moderate exercise a. Sports specific exercise: e.g. running drills in soccer b. Non-contact training drills: e.g. complex training drills 3. Full exercise a. Full contact practice: e.g. normal training activities b. Return to competition: e.g. normal game play *Activity definitions based on Zurich consensus statement
NO EXPOSURE	No physical activity (physical rest) within 7 days of enrollment
ASSESSMENTS	Standardized assessment conducted by trained research assistants 1. Demographic data and past medical history 2. Acute Concussion Evaluation Inventory: Injury characteristics 3. Post Concussion Symptom Inventory (PCSI): Pre-injury, current symptoms 4. Child Sports Concussion Assessment Tool 3rd Edition (SCAT3): Cognitive status, physical examination and balance Phone or web-based follow up at day 7 and 28. Completed by parent for 5-8 years, completed by patient if > 8 years.
OUTCOME	Persistent Post Concussive Symptoms (PPCS). Defined as ≥ 3 new or worsening individual symptoms at day 28 compared to pre-injury
DESIGN	Observational: Prospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)

Were patients similar for prognostic factors that are known to be associated with the outcome (or did statistical adjustments address the imbalance).	Yes. See Table 1. Propensity scoring was used to match for 43 variables that may be associated with early activity including all 20 indicators on the post-concussion symptom inventory. The matched analysis did not include 900 patients with early activity and 91 patients without early activity. The propensity scores were similar: Early activity patients (0.641) and no early activity patients (0.627).
Were the circumstances and methods for detecting the outcome similar?	Yes. Phone or web-based follow up occurred at days 7 and 28. Completed by parent for patients 5-8 years. Completed by patient if > 8 years of age. It is not clear if these patients were similar at baseline to those that completed the study.
Was follow-up sufficiently complete?	No. See Figure 1. 3,063 patients completed the ED phase of the study. 650/3,063 (21.2%) did not complete follow up. Therefore 2,413 were included in the primary analysis.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

N = 2,413
Mean age 11.8 years (60.7% male)

PHYSICAL ACTIVITY WITHIN 7 DAYS	
No early physical activity	736 (30.5%)
Any Early physical activity	1,677 (69.5%)
Light aerobic	32.9%
Sports specific	8.9%
Non-contact drills	5.9%
Full contact practice	4.4%
Return to competition	17.4%

PERSISTENT POST CONCUSSIVE SYMPTOMS AT 28 DAYS*			
	ABSOLUTE RISK		RISK DIFFERENCE
	Early Physical Activity	No Early Physical Activity	% (95% CI)
Matched	555 (28.7%)	554 (40.1%)	11.4% (5.5, 16.9%)
Unmatched	1,677 (24.6%)	736 (43.5%)	18.9% (14.7, 23.0%)
Light vs None	795 (31.4%)	736 (43.5%)	12.0% (7.2, 16.8%)
Moderate vs None	357 (24.4%)	736 (43.5%)	19.1% (13.2, 24.6%
Full contact vs None	525 (14.5%)	736 (43.5%)	29.0% (24.2, 33.5%)
*Defined as ≥ 3 new or worsening individual symptoms at day 28 compared to pre-injury			

Persistent Post-Concussive Symptoms at 7 DAYS
Prevalence: 1,387/2,413 (57.5%)
No Early Activity: 584/736 (79.5%)
Early Activity: 803/1,677 (48.0%)
RISK DIFFERENCE: 31.5%, 95% CI (27.6, 35.1%)

HOW PRECISE IS THE ESTIMATE OF THE RISK?
Given the large sample size, the confidence intervals for the risk difference and relative risks were relatively narrow.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Yes. Table 1 includes an extensive list of demographic characteristics. The large sample size and the inclusion of multiple centers likely make the study's results generalizability to the majority of ED patients meeting inclusion and exclusion criteria. Though I suspect there were a higher number of hockey related injuries in this Canadian population.
Was follow-up sufficiently long?	Yes. The primary outcome was the persistence of symptoms a 28 days post injury. This is the definition of persistent post concussive symptoms.
Is the exposure similar to what might occur in my patient?	Yes. The exposure was early physical activity. 69.5% of patients engaged in early physical activity though it is unclear what recommendations were given at ED discharge. It is likely that our patients have equally ignored out recommendations for physical and cognitive rest. This is particularly true for the student athlete whose sport is in season.
What is the magnitude of the risk?	In the unmatched analysis, 24.6% of the patients with early physical activity and 43.5% of the patients with no early physical activity had persistent post concussive symptoms at 28 days (Risk Difference: 18.9%, 95% CI (14.7, 23.0%)). The authors did not indicate if they considered this to be a clinically significant difference.
Are there any benefits that offset the risks associated with exposure?	In this study, there was a decrease in the risk of persistent post concussive symptoms at 28 days for those who participated in early physical activity.

CLINICAL BOTTOM LINE

BACKGROUND: Previous concussion guidelines recommended both cognitive and physical rest until symptom resolution and then a gradual resumption of activities as tolerated. However, these recommendations were based primarily on consensus as there is limited high quality evidence. The timing and degree of rest required for the optimal recovery remains unknown. Physical rest for the athlete results in removal from a life validating activity and physical deconditioning. Complete cognitive rest is not often feasible for the student.

CLINICAL QUESTION: In children 5-18 years of age presenting to the emergency department after an acute injury and who meet concussion criteria is physical activity within 7 days of injury when compared to no physical activity within 7 days, associated with an increased risk of persistent post concussive symptoms at 28 days?

DESIGN/RISK OF BIAS: This was a well-designed prospective cohort study that included 2,413 patients in the primary analysis. The authors identified a number of potential limitations. These include:

1. This was an observational study with a higher risk of potential bias than a randomized trial. The study determines an associated between two variables but does not prove causation,
2. It could not account for possible unmeasured confounders. Propensity matching can take the place of randomization but is based on measured confounders. However, propensity matching excluded 900 patients in the early activity group and 91 patients in the no early activity group.
3. It is not clear what recommendations were given at discharge regarding the timing of return to activity and discharge recommendations were not standardized across the 9 study centers
4. Outcome data relied upon parent or patients self-report
5. The timing and level of activity was not recorded
6. The presence or absence of activity only assessed before day 7 not between day 7 and 28 at the end of which the assessment of the primary outcome occurred.
7. The study did not account for cognitive activity/rest.

In addition, pre-study levels of physical activity was not measure. Those with higher baseline activity pre-injury would be more likely to resume a higher level of activity after injury. This would be particularly true for those during a sports season. Finally, 650/3,063 (21.2%) did not complete follow up.

PRIMARY RESULTS: 69.5% of patients engaged in early activity with the majority engaging in light aerobic activity (32.9%) though 17.4% returned to full competition. There was a statistically significant decrease in the proportion of patients with persistent post concussive symptoms in those who reported early physical activity. In the unmatched analysis, 24.6% of the patients with early physical activity and 43.5% of the patients with no early physical activity had persistent post concussive symptoms at 28 days (Risk difference: 18.9%, 95% CI (14.7, 23.0%)). A statistically significant difference occurred as well in the matched analysis (Risk Difference: 11.4%, 95% CI (5.5, 16.9%) and for each level of physical activity compared to no physical activity (see Table below). The authors did not specify what they considered to be a clinically significant difference.

PERSISTENT POST CONCUSSIVE SYMPTOMS AT 28 DAYS*			
	ABSOLUTE RISK		RISK DIFFERENCE
	Early Physical Activity	No Early Physical Activity	% (95% CI)
Matched	555 (28.7%)	554 (40.1%)	11.4% (5.5, 16.9%)
Unmatched	1,677 (24.6%)	736 (43.5%)	18.9% (14.7, 23.0%)
Light vs None	795 (31.4%)	736 (43.5%)	12.0% (7.2, 16.8%)
Moderate vs None	357 (24.4%)	736 (43.5%)	19.1% (13.2, 24.6%
Full contact vs None	525 (14.5%)	736 (43.5%)	29.0% (24.2, 33.5%)
*Defined as ≥ 3 new or worsening individual symptoms at day 28 compared to pre-injury			

APPLICABILITY: The large sample size and the inclusion of multiple centers likely makes the study's results generalizability to most ED patients meeting inclusion and exclusion criteria.

AUTHOR'S CONCLUSION: "Among children and adolescents aged 5 to 18 years with acute concussion, participation in physical activity within 7 days of acute injury compared with no physical activity was associated with lower risk of PPCS at 28 days. A well-designed randomized clinical trial is needed to determine the benefits of early physical activity following concussion."

POTENTIAL IMPACT: This was a well-designed study with potential limitations inherent to its observational design. Early physical activity within 7 days was associated with a statistically significant decreased in post-concussion symptoms at 28 days after injury. When patients with no or minimal symptoms at 7 days were excluded the decrease remained.

The consensus statement on concussion in sport (October 2016), (Brit J Sports Med 2017, PubMed ID: 28446457) makes the following statement regarding rest after concussion:

"The basis for recommending physical and cognitive rest is that rest may ease discomfort during the acute recovery period by mitigating post-concussion symptoms and/or that rest may promote recovery by minimising brain energy demands following concussion. There is currently insufficient evidence that prescribing complete rest achieves these objectives. After a brief period of rest during the acute phase (24-48 hours) after injury, patients can be encouraged to become gradually and progressively more active while staying below their cognitive and physical symptom-exacerbation thresholds (i.e., activity level should not bring on or worsen their symptoms). It is reasonable for athletes to avoid vigorous exertion while they are recovering. The exact amount and duration of rest is not yet well defined in the literature and requires further study."

FAST EXAMINATION:
UTILITY IN PEDIATRIC TORSO TRAUMA

In hemodynamically stable patients under the age of 18 with blunt torso trauma does the focused assessment with sonography for trauma examination (FAST) when compared to standard clinical care, decrease CT utilization, ED length of stay and hospital charges without an increase in missed intra-abdominal injuries?

Guillermo Alberto De Angulo, MD., Adriana Manikian, MD

August 2017

Holmes JF, Kelley KM, Wootton-Gorges SL, Utter GH, Abramson LP, Rose JS, Tancredi DJ, Kuppermann N

EFFECT OF ABDOMINAL ULTRASOUND ON CLINICAL CARE, OUTCOMES, AND RESOURCE USE AMONG CHILDREN WITH BLUNT TORSO TRAUMA: A RANDOMIZED CLINICAL TRIAL.

JAMA 2017 Jun 13;317(22):2290-2296.
PubMed ID: 28609532

STUDY DEFINITIONS	
POPULATION	Inclusion: Inclusion and exclusion criteria were designed to obtain a population with a 5% rate of intra-abdominal injury. < 18 years, hemodynamically stable with trauma within 24 hours of ED presentation meeting 1 of the following 4 criteria 1. Blunt torso trauma from a significant mechanism of injury: a. MVC: > 60 mph, ejection or rollover b. Automobile vs pedestrian or bicycle with automobile speed > 25 mph c. Falls > 20 feet in height d. Crush injury to the torso e. Physical assault to the abdomen 2. Blunt torso trauma with a decreased level of consciousness: GCS < 15 or age appropriate behavior. 3. Blunt trauma with extremity paralysis or multiple long bone fractures. 4. History or exam suggestive of intra-abdominal injury following blunt torso trauma of any mechanism (including those less severe that listed above) Exclusion: 1. Pre-hospital or ED age adjusted hypotension 2. Pre-hospital or ED GCS score < 9 3. Presence of abdominal seat belt sign 4. Penetrating trauma 5. Traumatic injury > 24 hours prior to ED presentation 6. Transfer to the ED from an outside facility with abdominal CT scan, diagnostic peritoneal lavage or previously performed laparotomy 7. Disease with intraperitoneal fluid: e.g. liver failure, ventriculoperitoneal shunt Setting: Single level 1 pediatric trauma center. 4/2012-5/2015
INTERVENTION	Focused abdominal sonography in Trauma (FAST examination) performed by MD's meeting ACEP certification criteria. 4 views: Morrison's pouch, splenorenal fossa, subxiphoid, pelvis (short/long axis) Classified as: Positive (any fluid), Negative (No fluids) and Indeterminate Reviewed by 1of 2 expert ultrasonographers blinded to clinical data
CO-INTERVENTIONS	ED physicians completed a standardized data collection form detailing patient history and physical examination findings and suspicion of intra-abdominal injury (IAI) as: < 1%, 1-5%, 6-10%, 11-50%, > 50% and change in decision to obtain a CT before and after the FAST examination
CONTROL	Standard trauma evaluation
OUTCOMES	Primary Outcomes: 1. Rate of abdominal CT use in the ED or during hospitalization 2. Missed intra-abdominal injuries diagnosed after the patient left the ED 3. ED length of stay 4. Hospital charges Secondary Outcomes (not prespecified): 1. Time to abdominal CT 2. Hospital length of stay 3. Physician suspicion of intra-abdominal injury before/after FAST examination.
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. The study inclusion and exclusion criteria included a representative sample of those presenting with a diagnostic dilemma. These were stable patients who had a mechanism of injury that could lead to intra-abdominal injury. The study excluded hemodynamically unstable patients. Some would argue that these are the patients most likely to benefit from the FAST exam. If these patient's hemodynamic instability is not corrected by fluid resuscitation, a FAST exam could be used as an indication for urgent laparotomy bypassing the need for a CT scan.
Did investigators compare the test to an appropriate, independent reference standard?	The reference standard (for missed intra-abdominal injury) that the study used was a CT scan or clinical follow up. FAST scans were compared to the CT scan when both were obtained. The decision to order a CT scan was at the discretion of the ED physician. If a CT scan was not obtained then the FAST results were compared to patient outcome assessed by phone follow up at 1 week (up to 6 attempts or review of the patient's electronic medical record and the trauma database if not reachable by phone.
Were those interpreting the test and reference standard blind to the other results?	No, the ED physicians were not blinded. However, the ED physicians completed the FAST exam prior to the CT scan if obtained. The expert sonologists who subsequently reviewed the FAST and the research coordinators assessing the patient outcomes were blinded to study group assignment.
Did all patients' regardless patients receive the same reference standard irrespective of the test results?	No. It would have been unethical for all patients to undergo a CT scan. CT scan were performed at the discretion of the ED physicians in both arms of the study. All patients, regardless of the treatment arm, received the same standard trauma evaluation. However, what constitutes a standard trauma was not clearly defined.
Were patients randomized?	Yes. Randomization was stratified by age into three cohorts (< 3 years, 3-9.99 years and 10-18 years). Within each of the three cohorts patients were randomized in blocks of 20.
Was randomization concealed?	Unclear. The article does not specifically state the randomization was concealed.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. See Table 1. The proportion of patients in each group were similar regarding: age, gender, mechanism of injury, GCS, pediatric trauma score, abdominal tenderness, MD suspicion of IAI and the proportion with IAI and IAI with free peritoneal fluid. Those eligible but not enrolled were similar regarding: age, gender and mechanism of injury but had a lower proportion with IAI (4.3 vs 5.4%) and IAI with free peritoneal fluid (3.1 vs 4.3%).

Was follow up complete?	See Figure 1: Consort Diagram. In the FAST group 54% (249/460) were admitted and 26% (121/460) were reached by telephone. In the Standard Care group 54% (251/465) were admitted and 27% (126/465) were reached by telephone. Therefore, approximately 20% of patients had follow up dependent on medical record or trauma registry review. Patients who followed up at another hospital could have been missed.
Were patients analyzed in the groups to which they were randomized?	Yes. All patients randomized to the study interventions were included in the primary analysis in the group to which they were randomized. 2 patients (0.4%) in the FAST group received Standard Care without a FAST examination. 12 patients (2.6%) in the Standard Care group had a FAST examination.

WHAT ARE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Demographic Data
N = 925 (FAST: 460, Standard Care: 465)
Age (mean ± SD): 9.7 ± 5.3 years (62% male)
GCS (median, IQR): 15 (15, 15)
Pediatric Trauma Score (median, IQR): 10 (10, 11) (PTS ≥ 8 out of 12 with 0% mortality)
Intra-abdominal injury (IAI): 50/925 = 5.4%, 95% CI (4.0, 7.1%)
IAI requiring laparotomy: 9/925 = 0.97%, 95% CI (0.44, 1.8%), (18% (9/50) of those with IAI)

Primary Outcome: 1. CT Scan Utilization
FAST: 52.4%
Standard Care: 54.6%
Risk Difference: 52.4 - 54.6% = -2.2, 95% CI (- 8.7, 4.2%)

FAST RESULT	NUMBER RESULT	NUMBER CT SCAN[2]
Positive	25	25
Negative	412	202
Indeterminate	14	14
Total	451[1]	241

1. 9/460 with 1. missing data for FAST interpretation (7) or did not have a FAST (2)
2. 14 with indeterminate FAST had a CT, Table assumes 25 with positive FAST also had a CT

44.8% (202/451) with a Negative Fast had a CT. Indications for CT not provided.

IAI with free peritoneal fluid on CT (n = 19)
FAST: Positive 5/19 (26.3%), Negative (52.6%), Indeterminate (21.1%)

Primary Outcome: 2. Rate of Missed IAI
FAST: 1/460 = 0.2% (-0.6, 1.2%). 1 patient. FAST (-), CT (-) in ED, CT (+) for grade 1 liver laceration on reread, returned for admission for observation and managed non-operatively

Primary Outcome: 3. LOS in the ED
FAST: 6.03 hours
Standard Care: 6.07 hours
Mean Difference: 6.03 - 6.07 = -0.04 hours, 95% CI (-0.47, 0.4 hours)

Primary Outcome: 4. Hospital Charges
FAST: $ 46,400
Standard Care: $ 47,800
Mean Difference: 46,400-47,800 = -1,200, 95% CI (-6,600, 4,300)

Secondary Outcomes

	FAST	STANDARD	DIFFERENCE (95% CI)
Laparotomy	1.5%	0.4%	1.1%, (-0.3, 2.7%)
Admission (total)	54.1%	54.0%	0.2% (-6.3, 6.6%)
Admission ICU (subtotal)	16.5%	16.3%	0.2% (-4.6, 5%)
Hospital Length of Stay	29.6 hours	40.2 hours	-10.7 (-19.7, -1.6 hours)*
*Statistically significant difference			

Change in Clinical Suspicion after FAST Exam (Figure 2)
FAST: Significant increase in proportion with suspicion of < 1% and < 5%.
72/460 (15.6%) moved to < 1 % clinical suspicion post-FAST
27/460 (5.9%) moved to between 1-5%,
9/460 (2.0%) moved to between 6-10%
1/460 (0.2% moved to between 11-50%

173 FAST patients with < 1% post FAST. 49/173 (28%) had a CT, 0 had an intra-abdominal injury

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

The authors specified the following as clinically significant differences in their sample size determination. The differences in the primary outcomes were neither statistically nor clinically significant by the authors criteria.
Decrease in CT rate by 10%
Decrease in ED length of stay by 1 hour
Decrease in hospital charges by 15%

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Unclear. 88% were general emergency medicine physicians all of which were ACEP certified in FAST and likely have considerable experience with FAST in their adult patients. Inter-rater reliability was moderate as evidenced by a kappa statistic of 0.45, 95% CI (0.3, 0.6).
Are the study results applicable to the patients in my practice?	Unclear. The standard of care for suspicion of intra-abdominal injury and criteria for laparotomy at this single institution are not described. The authors state that “no protocol for obtaining CT scans were in place”. It is also unclear if the ED physician or pediatric or trauma surgeon made the decision to obtain a CT of if it was a consensus decision.
Will patients be better off as a result of the test?	The authors conclude that FAST US did not improve clinical care, ED length of stay, CT scan rates or overall hospital charges. Unclear indications for CT and Issues with generalizability of this single center study limit the authors conclusion about the utility of the FAST examination in pediatric patients.

CLINICAL BOTTOM LINE

EDITORS NOTE: This study is a rare randomized clinical trial of the impact of a diagnostic test and is not a study of the diagnostic accuracy of the FAST examination. The critical article review form used is a compilation of the review forms for therapy and diagnostic testing.

BACKGROUND: Focused assessment with sonography for trauma can be used to evaluate patients with the goal of identifying hemoperitoneum associated with intra-abdominal injuries. When comparing CT and FAST examination the advantages for the FAST exam are availability at the bedside, rapid completion, ability for serial examinations, performance and interpretation by ED physicians and lack of radiation exposure. Studies in adult have shown that FAST has decreased CT rates, hospital length of stay, complications and hospital charges. However, there are fewer studies in the pediatric population.

CLINICAL QUESTION: In hemodynamically stable patients under the age of 18 with blunt torso trauma does the focused assessment with sonography for trauma examination (FAST) when compared to standard clinical care, decrease CT utilization, ED length of stay and hospital charges without an increase in missed intra-abdominal injuries?

DESIGN/RISK OF BIAS: This is a single center randomized non-blinded clinical trial. The primary intention to treat analysis included 925 pediatric patients with blunt torso trauma (FAST: 460, Standard Care: 465) who were hemodynamically stable. The study was well designed. However, standard of care at the institution was not clearly defined other that the statement that “no protocol for obtaining CT scans were in place”. The study would have benefited from clinicians documenting the indications for CT and who recommended the CT. If for example, the trauma surgeons did not trust the FAST exam interpretation the utility of FAST would be decreased.

Randomization was stratified by age into three cohorts (< 3 years, 3-9.99 years and 10-18 years) though the sample size precluded analysis of study outcomes in these cohorts. ED physicians were not blinded. However, the ED physicians completed the FAST exam prior to the CT scan if obtained. The expert sonologists who subsequently reviewed the FAST and the research coordinators assessing the patient outcomes were blinded to study group assignment. The CONSORT diagram indicates that approximately 20% of patients had follow up dependent on medical record or trauma registry review. If these patients followed up at another hospital intra-abdominal injury could have been missed.

PRIMARY RESULTS: A total of 50 patients (5.4% CI 4 to 7.1%) were diagnosed with intra-abdominal injuries, including 40 (80%, 95% CI 66 to 90%) who had intraperitoneal fluid found on an abdominal CT scan, and 9 patients (0.97%, 95% CI 0.44 to 1.8%) underwent laparotomy. The proportion of patients with abdominal CT scans was 52.4% (241/460) in the FAST group and 54.6% (254/465) in the standard care (Risk Difference: 95% CI, -2.2%, 95% CI (-8.7, 4.2%). The mean ED length of stay was 6.03 hours in the FAST group and 6.07 in the standard care group (Mean Difference: -0.04 hours, 95% CI (-0.47, 0.4 hours)

The clinical suspicion of intra-abdominal US rate after the FAST examination decreased in 68 patients. 44.8% (202/451) of patients with a Negative Fast had a CT. 28% (49/173) of patient s FA with a clinical suspicion of intraabdominal injury of < 1% after the FAST had a CT. None of the patients had an intra-abdominal injury. The indication for the CT in these patients were not presented.

APPLICABILITY: The standard of care for suspicion of intra-abdominal injury and criteria for laparotomy at this single institution are not described. The authors state that “no protocol for obtaining CT scans were in place”. In is also unclear if the ED physician or pediatric or trauma surgeon made this decision of if it was a consensus decision. 88% of those performing the ED FAST examination were general emergency medicine physicians all of which were ACEP certified in FAST and likely have considerable experience with FAST in their adult patients. It would be helpful to know the CT rate of adult trauma patients at the institution with similar pre-test probability. Finally, Inter-rater reliability of FAST interpretation was only moderate as evidenced by a kappa statistic of 0.45, 95% CI (0.3, 0.6).

Inclusion and exclusion criteria were designed to obtain a population with a 5% rate of intra-abdominal injury. The study prevalence of intraabdominal injury was 5.4%. The study results may not be generalizable to patients with lower or higher pretest probability of intraabdominal injury.
AUTHOR’S CONCLUSION: “Among hemodynamically stable children treated in an ED following blunt torso trauma, the use of the FAST examination compared with standard care only did not improve clinical care, including use of resources; ED throughput; intra-abdominal injuries; or hospital charges. These findings do not support the routine use of the FAST examination in this setting.”

POTENTIAL IMPACT: The primary utility of the FAST exam is to identify intraperitoneal fluid in a timely fashion, at the bedside in a non-invasive manner in the hemodynamically unstable patient so that they can go to laparotomy with the delay required for further imaging in CT scan. The potential utility of FAST in hemodynamically stable patients is to decreased CT usage in patients without another clear indication for CT scan (persistent abdominal pain/tenderness, seat belt sign). In addition, there may be some benefit of practicing the FAST examination in the more common hemodynamically stable patient so that the skill will be available in the rarer hemodynamically stable patient with blunt torso trauma.

Diagnostic tests are least useful when results of the test are discordant with pretest probability. For example, a negative FAST exam will likely not have an impact on clinical decision making in patients with clinical and laboratory findings consistent with a high probability of intraabdominal injury. The FAST exam is likely to have the greatest utility in hemodynamically stable patients in which there is a very low pretest probability of intra-abdominal injury. In this population. Serial FAST in conjunction with serial abdominal examination and laboratory testing could potentially decrease CT utilization. The reasons that approximately 45% of patients with a negative FAST and 28% of patients with a clinical suspicion of intraabdominal injury of < 1% had CT scans is unclear. It is also unclear why a decrease in clinical suspicion of intraabdominal injury after the FAST examination did not translate into decreases in CT usage. The authors acknowledge the potential lack of generalizable of a single center study and state that “a multicenter randomized clinical trial would more definitively answer the question regarding the utility of the FAST examination for injured children. A decision algorithm incorporating the FAST examination with physical examination and laboratory results would be helpful.

FAST EXAMINATION:
PEDIATRIC ACCURACY

In pediatric patients with acute blunt abdominal trauma, what is the diagnostic accuracy of the focused assessment with sonography in trauma (FAST) examination when compared to CT scan, intraoperative findings or clinical follow up in identifying those with and without intraabdominal injury (IAI) and intraabdominal injury requiring an intervention (IAI-I)?

Michael Mojica, M.D.

September 2017

Calder BW, Vogel AM, Zhang J, Mauldin PD, Huang EY, Savoie KB, Santore MT, Tsao K, Ostovar-Kermani TG, Falcone RA, Dassinger MS, Recicar J, Haynes JH, Blakely ML, Russell RT, Naik-Mathuria BJ, St Peter SD, Mooney DP, Onwubiko C, Upperman JS, Zagory JA, Streck CJ.

FOCUSED ASSESSMENT WITH SONOGRAPHY FOR TRAUMA IN CHILDREN AFTER BLUNT ABDOMINAL TRAUMA: A MULTI-INSTITUTIONAL ANALYSIS

J Trauma Acute Care Surg. 2017 Aug;83(2):218-224.
PubMed ID: 28590347

STUDY DEFINITIONS	
POPULATION	Inclusion: < 16 years, blunt abdominal trauma, within 6 hours of injury Exclusion: > 6 hours post injury CT obtained prior to arrival (transferred patients) Mechanism of injury: isolated head or extremity mechanism, burns, hanging, penetrating trauma, fall from same level Setting: 14 Level I Pediatric Trauma Centers, 7/2014-7/2015
DIAGNOSTIC TEST	FAST Examination: Machines used, technique/approach and sonographer training or skill level were not reported. Completed at trauma team discretion
REFERENCE STANDARD	Abdominal/Pelvic CT scan Intraoperative findings Follow up at 30 days or at time of hospital discharge
OUTCOME	Test characteristics for the identification of patients with intraabdominal injury (IAI) and intraabdominal injury requiring an intervention (IAI-I). Intraabdominal injury not defined Interventions defined as laparotomy or angioembolization Centers stratified as high (> mean FAST rate) and low (< mean FAST rate)
DATA	Standardized Data Collection Form History: Mechanism, trauma activation level, demographics, abdominal pain, nausea, vomiting Physical Examination: Abdominal exam, injury severity score Laboratory data* Imaging*: FAST, CT, Chest and pelvic XRAYS Management*: Intraoperative findings, transfusion requirements Disposition*: Admission to floor, ICU *Laboratory testing, imaging, management and disposition at treatment team discretion
DESIGN	Observational: Retrospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Yes. Pediatric patients with blunt abdominal trauma presenting to level 1 pediatric trauma centers were included. Patients could have both symptoms (abdominal pain, nausea, vomiting) and signs (abdominal tenderness, abdominal wall trauma (e.g. seat belt sign) but the presence of intra-abdominal injury was not known.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. Test characteristics are provided only for those patients who had a FAST examination and a CT scan (potential for verification bias). The proportion of patient who did not have a CT and who were available for clinical follow up was not reported.
Were those interpreting the test and reference standard blind to the other results?	Yes. The FAST exam was performed prior to the CT scan. It is unclear if those interpreting the CT or outcome assessors were aware of FAST exam findings.
Did investigators perform the same reference standard in all patients regardless of the results of the test under investigation?	No. Obtaining a CT scan in all patients would have been unethical. Intra-operative findings and clinical follow up were used as surrogate outcome measures. Clinical follow up may not identify all abdominal injury but would be more likely to identify intra-abdominal injury requiring an intervention. Importantly, not all patients had a FAST exam. 41% of the patients with a FAST exam had a CT compared to 46.1% who did not have a FAST exam and had a CT.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

Demographic Data
N = 2,188 (FAST: 829, No FAST 1,359)
Age (mean(SD)): 7.8 ± 4.6 years
Trauma Activation Level: I (17.5%), II (67.2%)
Mechanism: Motor vehicle collision (46.5%), pedestrian or cyclist struck by auto (19.7%)
Physical examination: 34% with an abnormal abdominal examination
Injury severity score (mean): 5, (1, 10). The ISS has a range of 0-75. Higher scores are associated with worse prognosis. Link: MD CALC: Injury Severity Score
Blood pressure: Normal = 97.3%
Glasgow Coma Scale: > 13 = 84.1%

FAST Exam Performed: 37.9% (829/2,188), Institution range 0.8 to 94.1%
CT Exam Obtained: 44.2% (967/2,188), Institution range 6.4 to 92.6%
CT Rate FAST patients: 41% (340/829)
CT Rate No FAST patients: 46.1% (852/1,848)
CT Rate Difference: 5.1%, 95% CI (1.0, 9,1%)

Patients who had both a FAST and CT
Intra-abdominal Injury: 28.5%
Intra-abdominal Injury Requiring Intervention: 7.9%

FAST AND CT OBTAINED: INTRAABDOMINAL INJURY (IAI)				
		IAI		
		YES	NO	
FAST	POSITIVE	27	21	48
	NEGATIVE	70	222	292
		97	243	340

TEST CHARACTERISTIC	CALCULATION	POINT ESTIMATE (95% CI)
Prevalence	97/340	28.5%
Sensitivity	27/97	27.8% (19.9, 37.5%)
Specificity	222/243	91.4% (87.2, 94.3%)
Predictive Value (+) Test	27/48	56.3% (42.3, 69.3%)
Predictive Value (-) Test	222/292	76% (70.8, 80.6%)
Likelihood Ratio (+) Test	(27/97)/(21/243)	3.2 (1.9, 5.4)
Likelihood Ratio (-) Test	(70/97)/(222/243)	0.79 (0.69, 0.90)

FAST AND CT OBTAINED: INTRAABDOMINAL INJURY REQUIRING INTERVENTION (IAI-I)				
		IAI-I		
		YES	NO	
FAST	POSITIVE	12	36	48
	NEGATIVE	15	277	292
		27	313	340

TEST CHARACTERISTIC	CALCULATION	POINT ESTIMATE (95% CI)
Prevalence	27/340	7.9%
Sensitivity	12/27	44.4% (27.6, 62.7%)
Specificity	277/313	88.5% (84.5, 91.6%)
Predictive Value (+) Test	12/48	25.0% (14.9, 38.8%)
Predictive Value (-) Test	277/292	94.9% (91.7, 96.9%)
Likelihood Ratio (+) Test	(12/27)/(36/313)	3.86 (2.29, 6.51)
Likelihood Ratio (-) Test	(15/27)/(277/313)	0.63 (0.45, 0.88)

95% confidence intervals calculated at the Centre for Evidence Based Medicine website: WEB LINK

Other Outcomes

Subset Analysis: No difference in FAST accuracy in patients with hypotension, abdominal tenderness or decreased Glasgow Coma Score

FAST Rate: No difference in accuracy high FAST centers (68.9%) and low FAST centers (78.1%)

No Correlation between FAST and CT Rate.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Unclear. Facility with ultrasound depends on correct set up of the machine, image acquisition, image interpretation and clinical application of the results. The training of the ultrasonographers in this study was not presented. There was a wide range of institutional ultrasound usage 0.8 to 94.1%. Inter-rater reliability was not assessed.
Are the study results applicable to the patients in my practice?	The inclusion of 14 level I pediatric trauma centers likely makes the study's results generalizable to similar settings. The rate of Intra-abdominal injury was 28.5% and of Intra-abdominal Injury requiring intervention was 7.9%. The test characteristics of ultrasound are subject to spectrum bias. For example, the sensitivity of ultrasound would improve in a population with a larger amount of intraabdominal hemorrhage.
[3]	Unclear. In a hemodynamically stable patient, a positive FAST would be an indication for CT. In a hemodynamically unstable patient, a positive FAST would be an indication for laparotomy. A negative FAST in a patient with a low pretest probability of intra-abdominal injury (normal vital signs, normal physical examination and laboratory tests) may allow for serial FAST and abdominal examinations. A negative FAST in a patient with a high pretest probability of intra-abdominal injury (abnormal vital signs, abnormal physical examination orlaboratory tests) would like still require a CT. A negative FAST failed to identify 75% of liver injuries, 57% of spleen injuries 69% of grade 3 or greater liver or spleen injuries. It is unclear however, if these patients had other indications for CT.
Will patients be better off as a result of the test?	Unclear. The test characteristics of the FAST exam to identify intraabdominal injuries and intraabdominal injuries requiring intervention are inadequate to rely solely on its results.

CLINICAL BOTTOM LINE

BACKGROUND: Focused assessment with sonography for trauma can be used to evaluate patients with the goal of identifying hemoperitoneum associated with intra-abdominal injuries. When comparing CT and FAST examination the advantages for the FAST exam are availability at the bedside with interpretation by ED physicians, rapid completion, ability for serial examinations and lack of radiation exposure. Studies in adult have shown that FAST can decrease CT rates, hospital length of stay, complications and hospital charges. However, there are fewer studies in the pediatric population.

CLINICAL QUESTION: In pediatric patients with acute blunt abdominal trauma, what is the diagnostic accuracy of the focused assessment with sonography in trauma (FAST) examination when compared to CT scan, intraoperative findings or clinical follow up in identifying those with and without intraabdominal injury (IAI) and intraabdominal injury requiring an intervention (IAI-I)?

DESIGN/RISK OF BIAS: The was a planned retrospective, secondary analysis of data prospectively collected for a previous study. This was a well-designed study with limitations inherent to its observational design. For example, the decision to perform a FAST examination was at the treating team's discretion as was the decision to perform a CT scan. Indications for imaging or operative intervention were not defined for the study and were not presented. The ultrasound machines, FAST technique and level of training of the ultrasonographers was not standardized and not reported.

This is a rare study of diagnostic test accuracy in which all of the patients did not have the diagnostic test. When comparing patients who had a FAST examination to those who did not (Table 1 and Table 2) there was no difference in demographic data, trauma activation level, presenting vital signs, Glasgow Coma Scale, abnormal abdominal examination, mean hematocrit, rates of intraabdominal injury or intraabdominal injury requiring intervention, need for transfusion, need for ICU admission or hospital length of stay. In those who had a FAST examination, there was a statistically higher rate of motor vehicle collisions (↑ 8.2%) and lower rate of fall greater than 10 feet (↓ 2.2%) and assaults (↓ 2.1%). The clinical significant of these differences is unclear.

Test characteristics are provided only for those patients who had a FAST examination and a CT scan (potential for verification bias). Intraoperative findings and clinical follow up were used as surrogate outcome measures. The proportion of patient who did not have a CT and who were available for clinical follow up was not reported.

PRIMARY RESULTS: The majority of patients were level II trauma activations involved in motor vehicle collisions. 97.3% had a normal blood pressure and 34% had an abnormal abdominal examination. A FAST examination was performed in 37.9% of patients but the institution range varied widely (0.8 to 94.1%). A CT Exam was obtained in 44.2% of patients. The CT rate also had a wide range by institution (6.4 to 92.6%). The rate of CT was statistically lower in those with a FAST exam (CT Rate Difference: 5.1%, 95% CI (1.0, 9,1%)) though the clinical significance of this difference is unclear.

Test characteristics are presented for those with a FAST examination only if a CT was obtained. The sensitivity for both intra-abdominal injury (27.8%) and intraabdominal injury requiring intervention (44.4%) were low. Specificities were higher. A negative FAST failed to identify 75% of liver injuries, 57% of spleen injuries 69% of grade ≥ 3 liver and spleen injuries. It is unclear however if these missed patients had other indications for CT.

TEST CHARACTERISTICS: PATIENTS WITH BOTH A FAST AND A CT		
	Intra-abdominal Injury (IAI)	Intra-abdominal Injury Requiring Intervention (IAI-I)
Prevalence	28.5%	7.9%
Sensitivity	27.8% (19.9, 37.5%)	44.4% (27.6, 62.7%)
Specificity	91.4% (87.2, 94.3%)	88.5% (84.5, 91.6%)
Predictive Value (+) Test	56.3% (42.3, 69.3%)	25.0% (14.9, 38.8%)
Predictive Value (-) Test	76% (70.8, 80.6%)	94.9% (91.7, 96.9%)
Likelihood Ratio (+) Test	3.2 (1.9, 5.4)	3.86 (2.29, 6.51)
Likelihood Ratio (-) Test	0.79 (0.69, 0.90)	0.63 (0.45, 0.88)

The FAST examination stratified a population with a 28.5% rate of intraabdominal injury into a high-risk group (52.6%) if the FAST was positive and a low risk group (24.0%) if the FAST was negative. The FAST examination stratified a population with a 7.9% rate of intraabdominal injury requiring intervention into a high-risk group (25.0%) if the FAST was positive and a low risk group (5.1%) if the FAST was negative. The presentation of test characteristics in patients without other indication for CT would have been helpful.

APPLICABILITY: The study's test characteristics are likely generalizable to patients with similar acuity meeting the study's inclusion and exclusion criteria. Ultrasound is user dependent. Facility with ultrasound depends on correct set up of the machine, image acquisition, image interpretation and clinical application. The training and experience of the ultrasonographers in this study was not presented. There was a wide range of institutional ultrasound usage (0.8 to 94.1%). Interestingly, FAST accuracy was not higher at institutions with a higher rate of FAST usage. Inter-rater reliability of image interpretation was not assessed.

Only 2.7% of patients of were hypotensive so the study's results are likely not generalized to this population. In addition, the test characteristics of ultrasound are subject to spectrum bias. For example, the sensitivity of ultrasound would improve in a population with a larger amount of intraabdominal hemorrhage.

AUTHOR'S CONCLUSION: "In conclusion, significant variability in FAST utilization exists among pediatric trauma centers. As currently used, FAST has a low sensitivity for IAI, misses IAI-I and rarely impacts management in pediatric blunt abdominal trauma. Furthermore, FAST use is not correlated with a decreased rate of abdominal CT imaging. Overall, these results support the limited use of FAST to triage hypotensive patients for IAI-I rather than as a substitute for abdominal CT. Further trials are needed to determine how to improve the sensitivity and negative predictive value of FAST, and which subset of children, if any, might benefit from FAST after blunt mechanism of injury"

POTENTIAL IMPACT: The primary utility of the FAST exam is to identify intraperitoneal fluid in a timely fashion, at the bedside in a non-invasive manner in the hemodynamically unstable patient so that they can go to laparotomy without the delay required for further imaging. The potential utility of FAST in hemodynamically stable patients is to decreased CT usage in patients without another clear indication for CT scan (persistent abdominal pain/tenderness, seat belt sign). In addition, there may be some benefit of practicing the FAST examination in the more common hemodynamically stable patient so that the skill will be available in the rarer hemodynamically stable patient with blunt torso trauma.

The FAST exam is likely to have the greatest utility in hemodynamically stable patients in which there is a very low pretest probability of intra-abdominal injury. The test characteristics of the FAST examination in primarily hemodynamically stable pediatric patients does not allow it to be used as the sole factor in clinical decision making. Serial FAST in conjunction with serial abdominal examination and laboratory testing could potentially decrease CT utilization.

In the article's discussion section, the authors provide a statement on the potential impact of the FAST examination in pediatrics. "Further research is needed to determine whether a combination of history and physical examination findings combined with presenting laboratory values and non-CT imaging results could potentially improve patient care and lead to more judicious use of abdominal CT scans. The role of the FAST examination in triaging patients to observation, abdominal CT or surgery beyond the other information available in the trauma bay remains unclear."

HEAD TRAUMA:
DECISION RULE DERIVATION (CATCH)

In patients < 16 years of age with blunt head trauma presenting to a Pediatric ED, do history and physical exam factors adequately identify those with and without brain injury on CT or the need the for neurologic intervention?

Vaishali Shah, M.D., Deborah Levine, M.D.
March 2010

Osmond MH, Klassen TP, Wells GA, Correll R, Jarvis A, Joubert G, Bailey B, Chauvin-Kimoff L, Pusic M, McConnell D, Nijssen-Jordan C, Silver N, Taylor B, Stiell IG; Pediatric Emergency Research Canada (PERC) Head Injury Study Group.

CATCH: A CLINICAL DECISION RULE FOR THE USE OF COMPUTED TOMOGRAPHY IN CHILDREN WITH MINOR HEAD INJURY.

CMAJ. 2010 Mar 9;182(4):341-8.
PubMed ID: 20142371

STUDY DEFINITIONS	
POPULATION	Inclusion: 0–16 years, presented to ED, acute minor head injury, within the past 24 hours, Glasgow Coma Scale in the ED ≥ 13. Blunt trauma to the head resulting in: witnessed loss of consciousness, definite amnesia, witnessed disorientation, persistent vomiting (two or more distinct episodes of vomiting 15 minutes apart) or persistent irritability in the emergency department (Children < 2 years) Exclusion: Penetrating skull injury or obvious depressed fracture, acute focal neurologic deficit, chronic generalized developmental delay, head injury secondary to suspected child abuse, returning for reassessment of a previously treated head injury, pregnant Setting: 10 Canadian Pediatric Tertiary Care Center ED's. 7/2001-11/2005
RULE PARAMETERS	Rule parameters: Patients assessed by staff physicians in the ED (Pediatrics, Emergency Medicine or Family Medicine or supervised ≥ PGY-2 residents). One-hour training session: 26 standardized clinical findings: history, general examination and neurologic status.
REFERENCE STANDARD	1. Neurologic Intervention: Death within 7 days due to head injury, need for: craniotomy, elevation of skull fracture, monitoring of intracranial pressure or insertion of an endotracheal tube for the treatment of head injury within 7 days. 2. Brain injury on CT: Any acute intracranial finding revealed on CT attributable to acute injury, including: closed depressed skull fracture, pneumocephalus. Excluding non-depressed skull fractures and basilar skull fractures. CT scan obtained a discretion of treating physician. If concern for injury, CT scan was read by a neurosurgeon and an additional radiologist CT considered negative if uncertainty remained. Patients not undergoing imaging classified as no clinically important brain injury if at 14 days: absent or mild headache, no complaints of memory or concentration problems, no seizure, no focal motor findings and return to usual daily activities Determined during a blinded, structured interview conducted by telephone
OUTCOMES	Rule Characteristics Potential reduction in CT utilization
DESIGN	Observational: Prospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. See Tables 3 and 4. The list of potential predictors is comprehensive.
Were all important predictors present in significant proportion of the study population?	Yes. See Tables 3 and 4. It would have been helpful to see a breakdown of patients who were greater and less than 2 years as well as the hematoma locations.
Were the outcome event and predictors clearly defined?	Yes. The outcome of need for neurologic intervention is clearly defined as: death within 7 days secondary to head injury or the need for surgical procedure or endotracheal intubation. Secondary outcome was brain injury on CT, attributable to acute injury. Predictors were fairly objective. The kappa statistics for the rule parameters range from 0.53 to 0.77.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Yes. The physician assessors recorded findings of the standardized assessment on data collection sheets before CT. Staff radiologists who interpreted the CT were blinded to the data form. Patients who did not undergo imaging were classified as having no clinically important brain injury if they met explicit criteria at 14 days and were assessed by a nurse who was unaware of the patient's predictor variables.
Was the sample size adequate (including an adequate number of outcome events)?	3,866 were included of which 159 (4.1%) had a brain injury on CT and 24 (0.6%) required neurosurgical intervention. There is no general rule for adequate sample size for recursive partitioning. The lower limit of the confidence intervals can be used to judge if sample size is adequate. For logistic regression, a general rule is 10 outcomes for each predictor. There were 4 predictors of neurosurgical intervention in the rule and 24 cases. There were 3 predictors of head injury on CT and 159 cases.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

CT performed: 2,043/3,866 (52.8%)
Prevalence Neurosurgical intervention: 24 (0.6%).
Prevalence Brain injury on CT: 159 (4.1%)
GCS: 14 = 7.3%, 13 = 2.5%
(See: Rule parameters in the clinical bottom line below)

CATCH Rule: Need for Neurologic Intervention
(1 of 4 high-risk rule parameters)
Sensitivity: 100.0%, 95% CI (86.2, 100%)
Predictive Value of a (-) Rule: 100%, 95% CI (99.9, 100 %)

CATCH Rule: CT Visible Brain Injury
(1 of 4 high-risk OR 3 medium risk rule parameters)
Sensitivity: 98.1%, 95% CI (94.6, 99.4%)
Predictive Value of a (-) Rule: 99.8%, 95% CI (99.5, 99.9%)

Predictive values calculated at the Centre for Evidence Based Medicine Website (LINK)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)

CATCH Rule: Need for Neurologic Intervention
(1 of 4 high-risk rule parameters)
Specificity: 70.2%, 95% CI (68.8, 71.6%)
Predictive Value of a (+) Rule: 1.6%, 95% CI (1.1, 2.4%)

CATCH Rule: CT Visible Brain Injury
(1 of 4 high-risk OR 3 medium risk rule parameters)
Specificity: 50.1%, 95% CI (45.2, 56.4%)
Predictive Value of a (+) Rule: 7.8%, 95% CI (6.7, 9%)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

Use of the rule for neurosurgical intervention would result in 30.2% of children with minor head injury having a CT. Use of the rule for a CT visible brain injury would result in 51.9% of patients with minor head injury having a CT**.** The CT rate for minor head injury in the study pediatric ED was 53% in 2005.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

Yes. In the internal validation set the 4 high-risk factors for neurologic intervention, the sensitivity was 97.9%, 95% CI: (97.8, 97.9%) and the specificity was 70.2%, 95% CI (70.1, 70.3%). For all seven factors determining the risk for brain injury, the sensitivity was 98.1%, 95% CI (98.0, 98.2%) and the specificity was 50.0%, 95% CI (50.0, 50.1%). These are similar to the primary results.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see appendix)	☐ I ☐ II ☐ III ■ IV This is a level IV clinical decision rule. The rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. A level IV rule requires further validation before it can be applied clinically.
Does the rule make clinical sense?	Yes. The rules make clinical sense. It includes factors we typically consider defining risk for head trauma.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	The kappa statistics for the rule parameters range from 0.53 – 0.77. Some of the predictors are somewhat subjective: history of worsening headache (Kappa: 0.55), suspected open or depressed skull fracture (Kappa 0.53) and GCS < 15 at two hours after injury (Kappa only provided for initial GCS: 0.58).
Is the rule applicable to the patients in my practice?	Yes, this study included ED patients at multiple sites.
Will the rule results change my management strategy?	No. Not until it can be broadly validated.
What are the benefits of applying the rule to my patients?	Applying the CATCH rule would identify most patients with injury on CT or need for neurologic intervention and could potentially decrease the head CT rate.
What are the risks of applying the rule to my patients?	The risk of applying the rule is that rarely, some patients with brain injury or requiring neurologic intervention may be missed.

CLINICAL BOTTOM LINE

BACKGROUND: There is controversy about which children with minor head injury need to undergo computed tomography (CT). Risks associated with unnecessary neuro imaging may be significant. Many clinical factors are involved in the decision to obtain a CT scan in pediatric patients with head trauma.

CLINICAL QUESTION: In patients < 16 years of age with blunt head trauma presenting to a Pediatric ED, do history and physical exam factors adequately identify those with and without brain injury on CT or the need the for neurologic intervention?

DESIGN/RISK OF BIAS: This is a prospective, multicenter derivation of a clinical decision rule in children with mild head trauma to identify those at high and medium risk for neurological intervention and injury on CT respectively. This study was well designed. Recursive partitioning was utilized to identify predictors of the outcomes. Only those parameters with a kappa statistic of > 0.5 and $p < 0.05$ in a univariable analysis were included.

PRIMARY RESULTS: The study included 3,866 patients, 52.8% of which had a head CT performed. CT revealed a brain injury in 159 (4.1%) patients and 24 (0.6%) of the patients underwent a neurologic intervention. The analysis identified 7 predictors. 4 high risk predictors of the need for neurologic intervention and 3 moderate risk predictors of brain injury on CT scan (see table below). Those without any of the high risk factors were at very low risk of requiring neurologic intervention (Predictive Value of a Negative Rule: 100%, 95% CI (0.0, 0.1%)). Those without any of the moderate risk factors were at very low risk of a brain injury on head CT (Predictive Value of a Negative Rule: 99.8%, 95% CI (99.5, 99.9%)).

CATCH: RULE CHARACTERISTICS

	Need for Neurologic Intervention[1]	CT Visible Brain Injury[2]
Prevalence	0.6%	4.1%
Sensitivity	100.0%, 95% CI (86.2, 100%)	98.1%, 95% CI (94.6, 99.4%)
Specificity	70.2%, 95% CI (68.8, 71.6%)	50.1%, 95% CI (48.5, 51.7%)
Predictive Value (-) Rule	100%, 95% CI (XX%)	99.8%, 95% CI (99.5, 99.9%)
Predictive Value (+) Rule	2.1%, 95% CI (1.4, 3.1%)	7.8%, 95% CI (6.7, 9%)
CT Rate	30.2%	51.9%

1. 1 of 4 high-risk rule parameters (See Appendix)
2. 1 of 4 high-risk OR 3 medium risk rule parameters (See Appendix)

Use of the rule for neurosurgical intervention would result in 30.2% of children with minor head injury having a CT. Use of the rule for CT visible brain injury would result in 51.9% of patients with minor head injury having a CT. There is a potential to decrease head CT utilization.

CANADIAN ASSESSMENT OF TOMOGRAPHY FOR CHILDHOOD HEAD INJURY (CATCH)	
CT OF THE HEAD IS REQUIRED ONLY FOR CHILDREN WITH MINOR HEAD INJURY* AND ANY ONE OF THE FOLLOWING FINDINGS:	
HIGH RISK (NEED FOR NEUROLOGIC INTERVENTION)	
1	Glasgow Coma Scale Score < 15 at two hours after injury (Kappa initial GCS: 0.58)
2	Suspected open or depressed skull fracture (Kappa 0.53)
3	History of worsening headache (Kappa: 0.55)
4	Irritability on examination (Kappa 0.67)
MEDIUM RISK (BRAIN INJURY ON CT SCAN)	
5	Any sign of basal skull fracture (e.g., hemotympanum, “raccoon” eyes, otorrhea or rhinorrhea of the cerebrospinal fluid, Battle’s sign) (Kappa 0.77)
6	Large, boggy hematoma of the scalp (Kappa 0.70)
7	Dangerous mechanism of injury (e.g., motor vehicle crash, fall from elevation ≥ 3 feet [≥ 91 cm] or 5 stairs, fall from bicycle with no helmet) (Kappa not provided)
*Minor head injury defined as: Injury within the past 24 hours, associated with witnessed loss of consciousness, definite amnesia, witnessed disorientation, persistent vomiting (more than one episode) or persistent irritability (in a child under two years of age) in a patient with a Glasgow Coma Scale score of 13–15.	

APPLICABILITY: The rule above appears sensible and easy to apply. However, the parameters of irritability and history of worsened headache may be subjective. Also, it is unclear what the utility of the rule would be in a non-ED setting. Only 277 (7.1%) of patients were less than 2 year of age and only 23 (8.3%) cases of brain injury were identified possibly limited the use of the rule to younger patients. Finally, the clinical significance of injuries identified on CT is questionable.

This is a level IV clinical decision rule. The rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. A level IV rule requires further validation before it can be applied clinically.

AUTHOR’S CONCLUSION: “The CATCH rule is a sensitive, prospectively derived clinical decision rule that has the potential to both standardize the need for CT and reduce the number of CT scans performed for children with minor head injury. Further studies are required to prospectively validate this rule in other pediatric cohorts.”

POTENTIAL IMPACT: There are some concerns that some of the predictors in the rule are somewhat subjective. Both the high and medium risk rule adequately identified children at high risk for neurological intervention and moderate risk of brain injury on CT with high sensitivities and negative predictive values. Further validation is required before it can be applied clinically.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

HEAD TRAUMA:
DECISION RULE DERIVATION (PECARN)

In patients < 18 years of age with non-trivial blunt head trauma presenting to a Pediatric Emergency Department and who are evaluated by head CT or clinical follow-up, do history and physical exam factors accurately identify those with and without clinically important traumatic brain injury?

Michael Mojica, M.D.
October 2009

Kuppermann N, Holmes JF, Dayan PS, Hoyle JD Jr, Atabaki SM, Holubkov R, Nadel FM, Monroe D,Stanley RM, Borgialli DA, Badawy MK, Schunk JE, Quayle KS, Mahajan P, Lichenstein R, Lillis KA, Tunik MG, Jacobs ES, Callahan JM, Gorelick MH, Glass TF,Lee LK, Bachman MC, Cooper A, Powell EC, Gerardi MJ, Melville KA, Muizelaar JP, Wisner DH, Zuspan SJ, Dean JM, Wootton, Gorges SL;
Pediatric Emergency Care Applied Research Network (PECARN)

IDENTIFICATION OF CHILDREN AT VERY LOW RISK OF CLINICALLY IMPORTANT BRAIN INJURIES AFTER HEAD TRAUMA:
A PROSPECTIVE COHORT STUDY.

Lancet. 2009 Oct 3;374(9696):1160-70.
PubMed ID: 19758692

STUDY DEFINITIONS	
POPULATION	Inclusion: < 18 years of age, blunt head trauma within 24 hours, GCS ≥ 14 Exclusion: Trivial mechanism: fall from ground level, walk, run into stationary object with no signs or symptoms other than scalp abrasions and lacerations, penetrating trauma, history of central nervous system tumor, preexisting neurologic disease, neuroimaging prior to presentation. Setting: 25 Children's Hospital EDs in the PECARN network. Derivation set: 6/2004-3/2006, Validation set: 3/2006-9/2006
RULE PARAMETERS	Standardized data collection process completed prior to results of imaging. 38 candidate variables were considered: Mechanism (13 factors), History (7 factors), Physical (9 factors), Other (5 factors).
REFERENCE STANDARD	1. CT at MD discretion interpreted by site faculty radiologists or study radiologist if inconclusive 2. Clinical follow-up of discharged patients. Standardized telephone surveys at 7-90 days post ED visit, evaluation of medical examiner records if unavailable 3. Hospital course for admitted patients Traumatic Brain Injury (TBI): Intracranial hemorrhage or contusion, cerebral edema,traumatic infarction, diffusive axonal injury, shearing injury, signs of brain herniation, diastasis of the skull, pneumocephalus or depressed skull fracture Clinically Important Traumatic Brain Injury (ciTBI): TBI above associated with: 1. Death 2. Neurosurgical intervention 3. Intubation for > 24 hours 4. Admission for > 48 hours
OUTCOME	Rule Characteristics: Derivation and validation sets Separate rules for < 2 years of age and ≥ 2 years of age Potential decrease in head CT Utilization
DESIGN	Observational: Prospective cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. (See Panel 1) The list of predictors is exhaustive. Adhered to STARD (STAndards for Reporting Diagnostic accuracy studies).
Were all important predictors present in significant proportion of the study population?	Unclear. (See Table 1 and 2, predictor prevalence by age category and study phase). Signs of basilar skull fracture seen in only 0.5% < 2 years and 0.7% ≥ 2 years. Only 3% of patients had a Glasgow Coma Scale of 14.
Were the outcome event and predictors clearly defined?	Yes. Outcome: Clinically important traumatic brain injury defined as TBI resulting in: 1. Death, 2. Neurosurgical intervention, 3. Intubation for > 24 hours or 4. Admission for > 48 hours. Predictors were objective. Most kappa statistics > 0.5 which is considered moderate.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Yes. The case report form was completed prior to results of CT if obtained. Follow-up on admitted and discharge patients was blinded to the presence of the predictors.
Was the sample size adequate (including an adequate number of outcome events)?	Yes. In general, 10 outcomes per rule parameter is considered adequate in logistic regression. Both of the age-based rules included 6 parameters. < 2 years: N = 8,502, 73 (0.9%) with ciTBI (Derivation) ≥ 2 years: N = 25,283, 215 (0.9%) with ciTBI (Derivation)

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT?

NOTE: Rule parameters are reported here as if a patient with ANY of the rule parameters is considered Positive and a patient with NONE of the rule parameters is considered Negative. This would be considered a “directive” rule. The authors instead recommend the use of an “assistive” rule (See Figure 3 and Appendix).

TBI: 5.2% (4.9, 5.6%), ciTBI: 0.9% (0.8, 1.0%)
ciTBI: Death = 0, Neurosurgery = 60, Intubated > 24 hours = 8, Admit > 48 hours = 308

< 2 Years Rule (Derivation, n = 8,502)
Sensitivity: 98.6%, 95% CI (92.6, 99.97%)
Specificity: 53.7%, 95% CI (52.6, 54.8%)
Predictive Value (-) Rule: 95% CI 99.9%, 95% CI (99.88, 99.99%)
Predictive Value (+) Rule: 1.8%, 95% CI (1.4, 2.3%)

Rule Parameters:
Altered mental status: GCS < 15 and other signs
Palpable skull fracture
Non-frontal scalp hematoma
Loss of consciousness for > 5 seconds
Severe mechanism of injury
Not acting normally as per parent

≥ 2 Years Rule (Derivation, n = 25,283)
Sensitivity: 96.7%, 95% CI (93.4, 98.7%)
Specificity: 58.5%, 95% CI (57.9, 59.1%)
Predictive Value (-) Rule: 99.95%, 95% CI (99.9, 99.99%)
Predictive Value (+) Rule: 2.0%, 95% CI (1.7, 2.2%)

Rule Parameters:
Altered mental status: GCS < 15 and other signs
Clinical signs of basilar skull fracture
History of loss of consciousness
History of vomiting
Severe mechanism of injury
Severe headache

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

Following the rules as a “directive” rule with all patients who are positive for any of the predictors undergoing CT would result in approximately 43% head CT rate. This could reduce the head CT rate in some settings (CDC data suggest a baseline CT rate of 50%) but may increase the CT rate in others (CT rate in the study was 35.3%). It is not possible to determine the impact of the rules on head CT utilization if they are used as “assistive” rules, as the authors recommend, because the heath care provider has an option for imaging or observation for patients with any of the lower risk factors.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

Yes. (See Figure 2) Results of both the derivation and validation sets were very similar. In some cases, the validation sets were more sensitivity and predictive value of a negative test were slightly higher though confidence intervals were wider due to the smaller sample size.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (See appendix)	☐ I ☐ II ☐ III ☐ IV ■? This is a difficult decision rule to classify. Technically the rules meet level IV criteria “Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods”. However, because this was a multicenter study using split samples it could be considered a level II rule “Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other and has not undergone an impact analysis.
Does the rule make clinical sense?	Yes. The rules do make clinical sense. Rule parameters are factors we typically consider defining risk for head trauma
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Some of the predictors are somewhat subjective. These include: scalp hematoma vs contusion, loss of consciousness of < 5 seconds, acting normally as per parent, the altered mental status definition of sleepy or agitated and headache severity. Inter-rater reliability of the predictors in the final rules were only moderate. The decision tree should include a legend defining altered mental status and severity of mechanism.
Is the rule applicable to the patients in my practice?	Yes. This study included ED patients at multiple sites throughout the U.S. Applicability to other clinical settings is unclear though the large sample size would appear to enhance generalizability of the rule.
Will the rule results change my management strategy?	The impact of the rule on management strategy will depend on the current approach to head trauma. The rules have the potential to standardize the approach to head trauma.
What are the benefits of applying the rule to my patients?	The rules would identify almost all the patients with ciTBI and in some settings, may decrease the CT rate
What are the risks of applying the rule to my patients?	Confidence intervals include the rare possibility of missing patients with ciTBI. In some settings, the rules may increase the CT rate.

CLINICAL BOTTOM LINE

BACKGROUND: Pediatric mild, blunt head trauma is a common occurrence. Traumatic brain injury requiring an intervention is rare. Risks associated with unnecessary neuroimaging may be significant. Prior studies have been small and conflicting with regards to risk factors and have not adequately addressed preverbal children. This prospective, multicenter Pediatric Emergency Care Applied Research Network (PECARN) study attempts to derive and validate clinical decisions rules in the preverbal and verbal child that identify those at low risk for clinically important traumatic brain injury (ciTBI) for which CT scans could be avoided.

CLINICAL QUESTION: In patients < 18 years of age with non-trivial blunt head trauma presenting to a Pediatric Emergency Department and who are evaluated by head CT or clinical follow-up do history and physical exam factors accurately identify those with and without clinically important traumatic brain injury?

DESIGN/VALIDITY: This study was well designed without major validity concerns. There is some concern that predictors and definitions utilized in the rules are somewhat subjective. Inter-rater reliability on some of the predictors is at best moderate. Clinically Important Traumatic Brain Injury (ciTBI) was defined as a traumatic brain injury associated with: 1. Death, 2. Neurosurgical intervention, 3. Intubation for > 24 hours or 4. Admission for > 48 hours.

PRIMARY RESULTS: 97% of patients had a Glasgow coma scale of 15 and 91% were discharged from the ED. The overall rate (both age groups combined) of traumatic brain injury (TBI) was 5.2%. The overall rate of clinically important TBI (ciTBI) was 0.9%. There were no deaths and few neurosurgical interventions in the study cohort. Only 0.14% had a TBI requiring neurosurgery. Most of those with clinically important traumatic brain injury were admissions for greater than 48 hours. It would be interesting to see the rule's performance if only death, neurosurgery and intubations for greater than 24 hours were the primary outcomes. The < 2-year-old rule included 8,502 patients of which 73 (0.9%) had ciTBI. The ≥ 2-year-old rule included 25,283 patients of which 215 (0.9%) had ciTBI.

Both rules adequately identified children at low risk for clinically important traumatic brain injury (ciTBI) as evidenced by high sensitivities and negative predictive values. The large sample sizes result in narrow (precise) confidence intervals. The negative predictive value for the < 2-year-old rule was 99.9%, 95% CI (99.88, 99.999%). The negative predictive of the ≥ 2-year-old rule was 99.95%, 95% CI (99.9, 99.99%). These values indicate a very low risk of traumatic brain injury in those with a negative rule. With the age groups and the validation and derivation sets combined only 10/42,419 (0.02% or 1 in 5,000) with ciTBI would have been missed by the rules.

The impact on CT rate may vary with clinical setting. Following the rules as a "directive" rule with all patients who are positive for any of the predictors undergoing CT would result in a CT rate of 43%. This could reduce the head CT rate in some settings (CDC data suggest a baseline CT rate of 50%) but may increase the CT rate in others (Study CT rate was 35.3%). It is not possible to determine the impact of the rules on head CT utilization if they are used as "assistive" rule, as the authors recommend, because the caregiver has an option for imaging or observation.

APPLICABILITY: The rule appears sensible and easy to apply. The subjectivity of some predictors may limit its usefulness and it is recommended that rules definitions for signs of altered mental status and mechanism of injury accompany the decision algorithm. The rules appear generalizable to a large variety of children though the applicability to non-ED settings is unclear. This stage of this decision rule is difficult to classify using the standard criteria for rule level (See Appendix). Technically it meets level IV criteria “Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods”. However, because this was a multicenter study using split samples it could be considered a level II rule “Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other and has not undergone an impact analysis.” Level II rules can be “used in a wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve.”

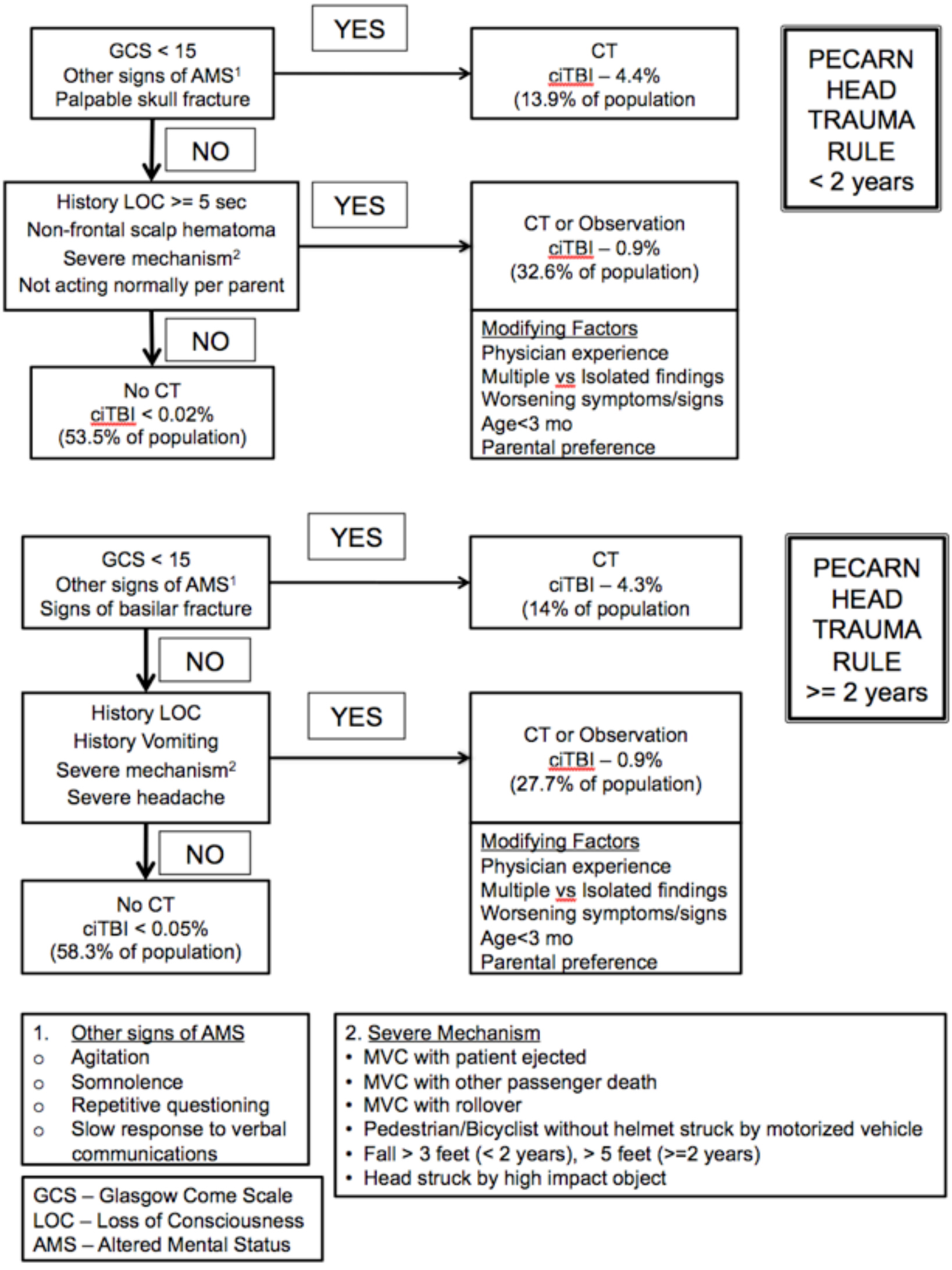
AUTHOR’S CONCLUSION: “Overall, in this study of more than 42,000 children with minor blunt head trauma, we derived and validated highly accurate prediction rules for children at very low risk of clinically important traumatic brain injuries for whom CT scans should be avoided. Application of these rules could limit CT use, protecting children from unnecessary radiation risks. Furthermore, these rules provide the necessary data to assist clinicians and families in CT decision making after head trauma.”

POTENTIAL IMPACT: This is likely to be the definitive study on pediatric head trauma for a long time to come. It would be helpful to include the rule parameters and definitions as well as head CT radiation exposure levels into decision support instruments. An impact analysis would be helpful to determine the rules ultimate effect on head CT utilization rates.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

APPENDIX: PECARN HEAD TRAUMA CLINICAL DECISION RULES



1. Other signs of AMS
   - Agitation
   - Somnolence
   - Repetitive questioning
   - Slow response to verbal communications

GCS – Glasgow Come Scale
LOC – Loss of Consciousness
AMS – Altered Mental Status

2. Severe Mechanism
   - MVC with patient ejected
   - MVC with other passenger death
   - MVC with rollover
   - Pedestrian/Bicyclist without helmet struck by motorized vehicle
   - Fall > 3 feet (< 2 years), > 5 feet (>=2 years)
   - Head struck by high impact object

HEAD TRAUMA:
DECISION RULE IMPACT (PECARN)

In pediatric patients with minor, non-trivial head trauma and who are at very low risk for clinically important traumatic brain injury by the PECARN head trauma clinical decision rules, does an electronic medical record based clinical decision support tool that provides classification of the patient as very low risk as well as a quantitative estimate of the risk of clinically important traumatic brain injury, reduce the utilization of non-contrast head CTs?

Sheri-Ann Wynter, M.D., Alvira Shah, M.D.
May 2017

Dayan PS, Ballard DW, Tham E, Hoffman JM, Swietlik M, Deakyne SJ, Alessandrini EA, Tzimenatos L, Bajaj L, Vinson DR, Mark DG, Offerman SR, Chettipally UK, Paterno MD, Schaeffer MH, Wang J, Casper TC, Goldberg HS, Grundmeier RW, Kuppermann N; Pediatric Emergency Care Applied Research Network (PECARN).Clinical Research on Emergency Services and Treatment (CREST) Network.; and Partners Healthcare; Traumatic Brain Injury-Knowledge Translation Study

USE OF TRAUMATIC BRAIN INJURY PREDICTION RULES WITH CLINICAL DECISION SUPPORT.

Pediatrics. 2017 Apr;139(4).
PubMed ID: 28341799

STUDY DEFINITIONS	
POPULATION	Inclusion: <18 years, minor blunt head trauma (Glasgow Coma Scale 14 or 15), ED presentation within 24 hours of trauma Exclusion: Penetrating trauma, brain tumors, known coagulopathy, ventricular shunts, preexisting neurologic disorders complicating assessments, previous neuroimaging obtained at an outside hospital, trivial trauma (mechanism: fall from ground level, walk, run into stationary object) with no signs or symptoms other than scalp abrasions and laceration. Setting: 13 EDs (5 Pediatric ED, 8 General ED), 11/2011-6/2014
INTERVENTION	Template with decision rule parameters completed in electronic medical record generated a clinical decision support tool that included: 1. If patient met the age-specific PECARN prediction rule very low risk criteria 2. Recommendation that CT was not indicated if met very low risk criteria 3. Risk estimate of clinically important traumatic brain injury 4. Links to prediction rule criteria and publication
CONTROL	1. 1 Pediatric ED and 1 General ED without the intervention served as controls 2. Each ED served as its own control in a pre-post implementation analysis
OUTCOME	Primary Outcome: Change in CT rate: 1. Patients at very low risk of ciTBI 2. Patients not at very low risk of ciTBI. Stratified by age and ED type Secondary Outcomes: 1. Patients with ciTBIs not identified on the initial ED visit 2. Length of stay (LOS) in the ED for discharged patients. 3. Sensitivity of PECARN rules to identify ciTBI Traumatic Brain Injury (TBI) on CT: Acute, traumatic intracranial finding and/or a skull fracture depressed by at least the width of the skull Clinically Important Traumatic Brain Injury (ciTBI): TBI on CT associated with: 1. Death 2. Neurosurgical intervention 3. Intubation > 24 hrs 4. Admit > 48 hrs.
DESIGN	Interventional: Non-randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
Was the implementation of the rule randomized?	No. Sites were selected to receive clinical decision support in a nonrandom fashion. Two ED's not participating in the impact analysis served as controls. In addition, each site served as its own control in a pre-post implementation analysis.
Was it a before-after design? If yes, how long a period post implementation was assessed?	The CT utilization rate was analyzed in a pre-post design. That is prior to and after the implementation of the clinical decision support tool. The CT rate prior to implementation was assessed for a mean of 14.1 months (range 9.6-15.7 months). The CT rate post implementation was assessed for a mean of 12.1 months (range 10.1-15.7 months).
What was the setting in which the rule was implemented? Does the setting(s) represent a wide spectrum of severity of disease?	The rule was implemented in 4 PECARN pediatric ED sites that had the same electronic health record (EPIC) and at 6 general ED sites (2 paired due to physician staffing and 2 unpaired) in the northern California Kaiser Permanente ED research network. All general EDs and 2 of the pediatric EDs were not a part of the derivation or validation of the prediction rules. There were patients who met PECARN TBI prediction rule very low risk criteria (43-47%), intermediate risk (33-36%), and high risk (11-11%), representing the spectrum of severity of TBI. The prevalence of clinically important traumatic brain injury was 0.7% (compared to 0.9% for the derivation and validation study).
What was the strategy for implementing the rule?	For each eligible patient, clinicians (attending physicians, fellows, residents, nurses, nurse practitioners, or physician assistants) completed a blunt head trauma data collection template in the electronic medical record that included all the decision rule clinical predictors. This was specifically designed for the study. The data entered into the template generated the clinical decision support tool that included an estimate of the risk of ciTBI, the risk category for ciTBI, and whether a head CT was recommended.
What training was required to utilize the implementation strategy?	Site physicians and informatics specialists were designated to train and encourage the staff.

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? HOW DOES THIS COMPARE TO THE POTENTIAL RULE CHARACTERISTICS DESCRIBED IN THE DERIVATION AND VALIDATION OF THE RULE?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? HOW DOES THIS COMPARE TO RULE CHARACTERISTICS DESCRIBED IN THE DERIVATION AND VALIDATION OF THE RULE?

NOTE: The rule characteristics below are for the PECARN rule defined as negative (no parameters present) and positive (any parameter present). This is not how the rule was intended to be utilized but is used here to allow for comparison of the rule characteristics of the impact and derivation studies. The data combines the < 2 year and ≥ 2 years rules.

IMPACT ANALYSIS	ciTBI		
	YES	NO	
ANY PARAMETER	111	9,042	9,153
NO PARAMETERS	3	7,479	7,842
	114	1,6521	16,635

	DERIVATION	**IMPACT**
Prevalence	0.9%	0.7%
Sensitivity	96.9% (94.2, 98.4%)	97.4% (92.5, 99.1%)
Specificity	57.3% (56.7, 57.8%)	45.3% (44.5, 46%)
Predictive Value (+) Rule	1.9% (1.7, 2.2%)	1.2% (1.0, 1.5%)
Predictive Value (-) Rule	100% (99.9, 100%	100% (99.9, 100%)

HOW DID IMPLEMENTATION OF THE RULE IMPACT RESOURCE UTILIZATION? HOW DOES THAT COMPARE TO THE POTENTIAL IMPACT DESCRIBED IN THE DERIVATION AND VALIDATION OF THE RULE?

ADJUSTED ODDS RATIO (*statistically significant)
All intervention EDs: 0.72, 95% CI (0.53, 0.99)*
Pediatric Control ED: 1.85, 95% CI (0.69, 4.98)
General Control ED: 0.35, 95% CI (0.16, 0.17)*

The tables below present an unadjusted absolute risk difference in the CT rate (ARD = CT rate Pre – CT rate Post). This was not presented by the authors but is easily calculated from the data provided. The authors defined a clinically significant reduction in the CT rate to be 7% in their sample size determination.

CT RATE: PATIENTS AT VERY LOW RISK (TABLE 3)			
AGE	PRE	POST	RISK DIFFERENCE (95% CI)
All	5.3%	4.2%	1.1% (0.1, 2.1%)
< 2 Years	6.8%	4.3%	2.5% (0.2, 4.9%)
≥ 2 Years	5.0%	4.2%	0.8% (-0.3, 1.8%)

CT RATE: PATIENTS NOT AT VERY LOW RISK (TABLE 5)			
SETTING	PRE	POST	RISK DIFFERENCE (95% CI)
Intervention EDs	36.5%	35.6%	1.3% (-0.9, 3.6%)
Control Pediatric ED	36.5%	31.4%	5.1% (-3.6, 13.7%)
Control General ED	36.9%	44.4%	-7.5% (-19, 4.2%)

CT RATE: PATIENTS AT VERY LOW RISK (TABLE 2)			
SETTING	PRE	POST	RISK DIFFERENCE (95% CI)
All Intervention EDs	5.3%	4.2%	1.1% (0.1, 2.1%)
Intervention PED	6.7%	5.0%	1.6% (0.3, 3.0%)
Intervention GED	2.8%	3.2%	0.3% (-1.0, 1.5%)
Control Pediatric ED	1.6%	2.9%	1.3% (-0.9%, 3.6%)
Control General ED	7.1%	2.6%	4.5% (1.3, 8.1%)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see appendix)	■ I ☐ II ☐ III ☐ IV This is a level I clinical decision rule. Derivation, broad validation and an impact analysis has been completed. A level I rule can be used in wide variety of settings with confidence.
Is the strategy to implement the rule used in the study applicable to your practice setting? What are the perceived barriers to implementation?	The strategy used to implement the PECARN rules is applicable to some of our practice settings where the electronic health record used is EPIC. It is unclear if the clinical decision support tool could be easily implemented into other electronic medical records. It is very unlikely, in our setting, that nurses would enter the primary data that included the rule parameters on which the clinical decision support tool output was generated.
What are the benefits of applying the rule to my patients?	The rules would identify almost all the patients with clinically important traumatic brain injury and may decrease CT utilization minimally.
What are the risks of applying the rule to my patients?	Confidence intervals include the rare possibility of missing patients with clinically important traumatic brain injury.

CLINICAL BOTTOM LINE

BACKGROUND: The PECARN head trauma decision rules have been derived and validated in a prior prospective multicenter cohort study of over 42,000 patients with clinical predictors for two age groups, children less than 2 years of age and those 2-18 years of age with non-trivial, presenting with mild blunt head trauma and GCS 14 to 15 presenting within 24 hours of the acute trauma. The rules will likely be the definitive decision instrument to determine the need for imaging for pediatric patients with non-trivial head trauma for some time to come. The primary goal of a decision rule is to accurately identify patients with the target condition (clinically important traumatic brain injury). The secondary goal is to reduce resource utilization (CT rate). The impact on CT rates after of implementing the PECARN head trauma rules have not been conclusively assessed. A clinical decision support tool that is integrated into the electronic medical record could facilitate adoption of the rule.

CLINICAL QUESTION: In pediatric patients with minor, non-trivial head trauma and who are at very low risk for clinically important traumatic brain injury by the PECARN head trauma clinical decision rules do an electronic medical record based clinical decision support tool that provides classification of the patient as very low risk as well as a quantitative estimate of the risk of clinically important traumatic brain injury, reduce the utilization of non-contrast head CT?

DESIGN/RISK OF BIAS: This study was a multicenter, prospective, impact analysis of the PECARN head trauma decision rules. The aim of the study was to assess the impact of a clinical decision support tool that was integrated into the medical record to decreased the head CT rate in patients at very low risk for clinically important traumatic brain injury. The study included 13 study centers, 5 of which were pediatric ED's and 8 were general ED's. Study centers served as their own control site in a pre-post implementation analysis. In addition, a pre-post analysis was carried out in two centers that did not have the intervention (controls) in order to account for changes in the CT rate over time that could occur for reasons other than the intervention. The primary analysis on CT rate included 7,842 patients at very low risk of clinically important traumatic brain injury (Table 2).

This was a well-designed study with few validity concerns. The study centers were not selected randomly. In addition, it would have been helpful to present the outcomes based on the three categories of the decision rules (high risk, intermediate risk and very low risk) rather than dichotomously as very low risk and not very low risk (combining the intermediate and high-risk groups). It is unclear if those who completed the template were the same as those who viewed the clinical decision support tool and those ordering providers the CT. The study did not control for other possible confounders such as the culture of the sites (e.g. Organizational initiatives to reduce CT use such as Image Gently, subspecialist and family requests for imaging) though use of a paired design with each study center assessed pre-CT rate to their post CT rate could limit the influence of these differences.

PRIMARY RESULTS: When all intervention EDs were analyzed, there was a statistically significant decrease in the rate of CT after implementation of the clinical decision support tool with an adjusted odds ratio of 0.72, 95% CI (0.53, 0.99). The CT rate pre-implementation was 5.3% and post-implementation was 4.2% for an unadjusted absolute difference in CT rate of 1.1%, 95% CI (0.1, 2.1%). While this is statistically significant its clinical significance is unclear. The authors defined a clinically significant reduction in the CT rate to be 7% in their sample size determination. This was based on an estimated pre-intervention CT rate of 14%. The average Pre-intervention CT rate in the intervention ED's was 5.3% and only 3 of the 8 intervention ED's had a pre CT rate greater than 7%. A decreased CT rate

of 7% could not have been achieved in the analysis for all intervention EDs and in 5 of the 8 individual intervention EDs. The authors attribute this to “passive diffusion” of the PECARN rules and it is certainly possible that the rules were used to some extent prior to the study. This would decrease the likelihood of demonstrating a decrease in CT utilization after implementation of the intervention.

The implementation of the rule did not lead to an increase in missed clinically important traumatic brain injury. None of the 3 patients with missed ciTBI underwent neurosurgery and were all from one site. These 3 patients either had concern for non-accidental trauma, had risk factors not identified on the template, or did not have the template completed by an attending physician. The median length of stay after clinical decision support implementation increased in 7 of the 8 intervention sites by 7 to 15 minutes.

	DERIVATION	IMPACT
Prevalence	0.9%	0.7%
Sensitivity	96.9% (94.2, 98.4%)	97.4% (92.5, 99.1%)
Specificity	57.3% (56.7, 57.8%)	45.3% (44.5, 46%)
P Value (+)	1.9% (1.7, 2.2%)	1.2% (1.0, 1.5%)
P Value (-)	100% (99.9, 100%	100% (99.9, 100%)
Rule characteristics in this table are based on 1. Combing both age groups, 2. Interpretation of the rule as positive if any predictor was present and negative if no predictors were present. This is not how the rule is intended to be interpreted and is used here only for comparison of the derivation and impact rule characteristics.		

CT RATE: PATIENTS AT VERY LOW RISK (UNADJUSTED)			
SETTING	PRE	POST	RISK DIFFERENCE (95% CI)
Intervention EDs	5.3%	4.2%	1.1% (0.1, 2.1%)
Intervention PED	6.7%	5.0%	1.6% (0.3, 3.0%)
Intervention GED	2.8%	3.2%	0.3% (-1.0, 1.5%)
Control Pediatric ED	1.6%	2.9%	1.3% (-0.9%, 3.6%)
Control General ED	7.1%	2.6%	4.5% (1.3, 8.1%)
AGE	PRE	POST	RISK DIFFERENCE (95% CI)
< 2 YEARS	6.8%	4.3%	2.5% (0.2, 4.9%)
≥ 2 YEARS	5.0%	4.2%	0.8% (-0.3, 1.8%)

APPLICABILITY: This was a multicenter impact analysis that included 13 emergency departments. The inclusion of both pediatric EDs and general ED’s make the study applicable to ED populations. There were varying providers who completed the head trauma template for this study, which could be a source of bias, as some sites used nurses more than other sites where a mid-level or physician completed the form. No measure of interrater reliability was presented. In 2 of 3 patients missed by the rule intentional head trauma was a concern. Because the less than 2-year-old rule is dependent on a parental assessment of status and a clear description of the mechanism of injury, the rule is not generalizable to patients with suspected non-accidental trauma.

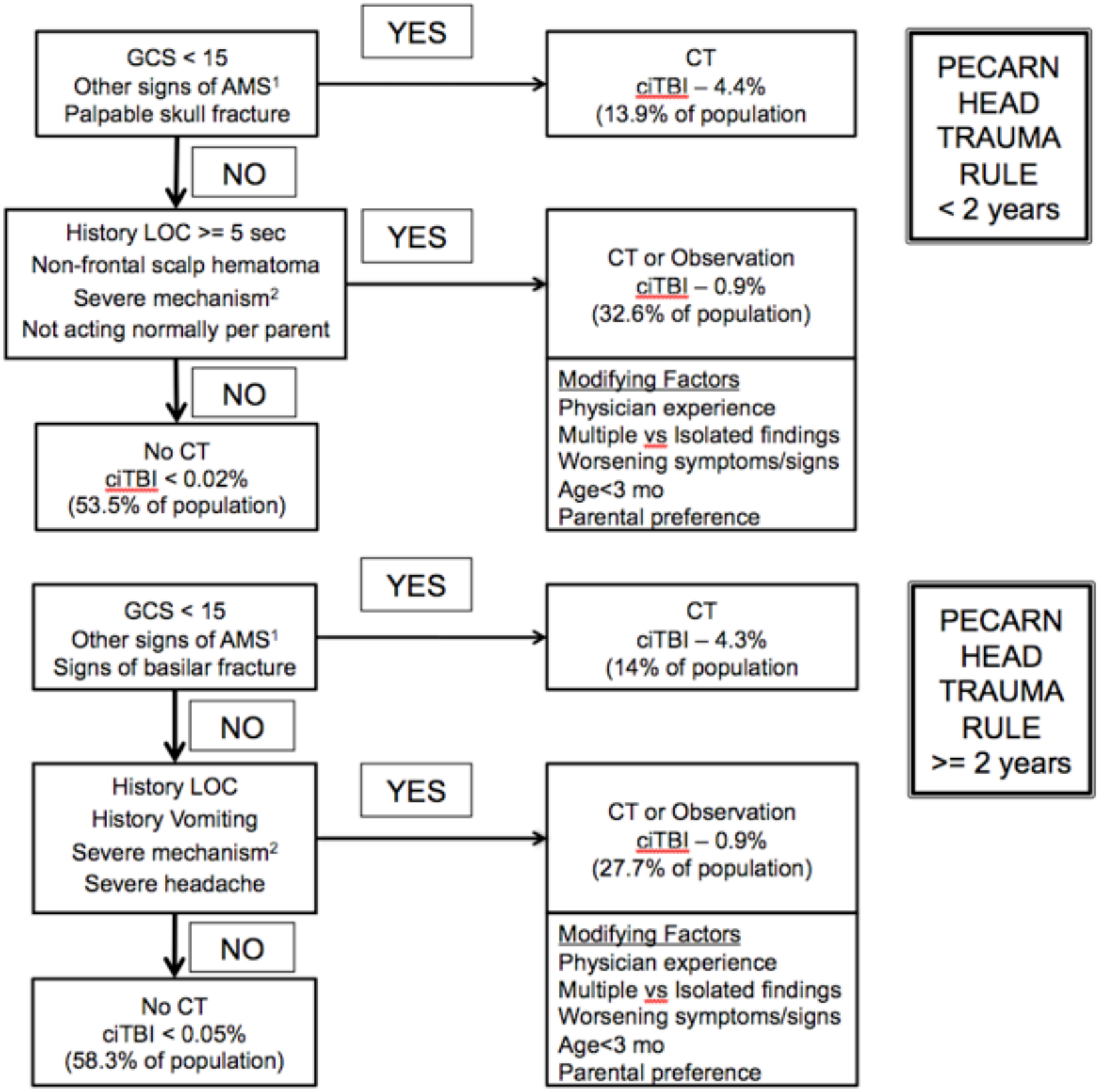
AUTHOR'S CONCLUSION: "The implementation of traumatic brain injury prediction rules and provision of risks of clinically important traumatic brain injury by using computerized Clinical Decision Support was associated with modest but variable decreases in rates of CT use for children at very low risk of clinically important traumatic brain injury and for all children with minor blunt head trauma, without increasing the rate of missed injuries. However, decreased CT rates were inconsistent across study sites and secular trends were noted."

POTENTIAL IMPACT: Ideally, the CT rate in the very low risk group should be 0% but factors other than the rule parameters may influence the decision to obtain a CT. The study demonstrated small and inconsistent decreases in CT utilization without a corresponding increase in those with clinically important traumatic brain injury who were missed. Due to the concern for radiation exposure increasing the risk of subsequent cancer even a small decrease in CT utilization may beneficial if it is not associated with an increased risk of missing patients with a clinically important traumatic brain injury.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

APPENDIX: PECARN HEAD TRAUMA RULES (DERIVATION POPULATION)



1. Other signs of AMS
   - Agitation
   - Somnolence
   - Repetitive questioning
   - Slow response to verbal communications

GCS – Glasgow Come Scale
LOC – Loss of Consciousness
AMS – Altered Mental Status

2. Severe Mechanism
   - MVC with patient ejected
   - MVC with other passenger death
   - MVC with rollover
   - Pedestrian/Bicyclist without helmet struck by motorized vehicle
   - Fall > 3 feet (< 2 years), > 5 feet (>=2 years)
   - Head struck by high impact object

HEAD TRAUMA:
ICU ADMISSION DECISION RULE DERIVATION

In pediatric patients with minor traumatic brain injury and intracranial hemorrhage and who do not require a critical care intervention in the field or in the emergency department, can clinical and radiologic findings identify those at low risk for requiring a critical care intervention during their inpatient stay?

Guillermo De Angulo, M.D., Jeffrey Fine, M.D.
December 2016

Burns EC, Burns B, Newgard CD, Laurie A, Fu R, Graif T, Ward CS, Bauer A, Steinhardt D, Ibsen LM, Spiro DM.

PEDIATRIC MINOR TRAUMATIC BRAIN INJURY WITH INTRACRANIAL HEMORRHAGE: IDENTIFYING LOW-RISK PATIENTS WHO MAY NOT BENEFIT FROM ICU ADMISSION

Pediatr Emerg Care. 2016 Oct.
PubMed ID: 27798539

STUDY DEFINITIONS	
POPULATION	Inclusion: < 18 years, evaluated in ED (primarily or after transfer), diagnosis of traumatic intracranial injury based on head CT prior to ED disposition Exclusion: Non-traumatic injury, penetrating trauma, directly admitted, not admitted, coagulopathy, traumatic brain injury without hemorrhage, received a critical care intervention in the field or in the ED, Setting: Single Children's Hospital ED and PICU, 3/2008-8/2013
RULE PARAMETERS	Review of medical records using a structured data collection form: 14 clinical and radiologic variables based on prior literature or biologic plausibility
REFERENCE STANDARD	Critical care interventions performed at any time during admission: Assisted ventilation, hyperosmolar therapy, vasoactive medication use, blood product transfusion, invasive monitoring, cardiopulmonary resuscitation, management of arrhythmia, interventional angiography, neurosurgical intervention (See Appendix for definitions)
OUTCOME	Rule characteristics Potential reduction in ICU admission
DESIGN	Observational: Retrospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. Table 4. 14 clinical and radiologic variables based on prior literature or biologic plausibility were included as potential predictors.
Were all important predictors present in significant proportion of the study population?	No. Table 3. The following candidate variables were infrequently present. Focal neurologic exam (7.7%), pneumocephalus (8.1%), midline shift (6.4%), depressed skull fracture (14.1%), epidural and/or intraventricular hemorrhage (11.8%) and base of skull fracture (3%). The absence of midline shift or depressed skull fracture were independent predictors of risk of critical care intervention.
Were the outcome event and predictors clearly defined?	Yes. Table 1: Mechanism definitions, Table 2: Critical Care Interventions. See Appendix. The predictor of "other injuries" was divided into: none, extremity only or more than extremities. What type of injury and their severity were not reported.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	No. Those determining the need for a critical intervention were not blinded. Assessment of predictors occurred prior to the need for critical care intervention.
Was the sample size adequate (including an adequate number of outcome events)?	Unclear. 296 patients of which 29 required critical care interventions. 4 independent predictors were identified. In general, logistic regression requires 10 outcomes for each predictor. The requirement for recursive partitioning is less clear.

WHAT ARE THE RESULTS?

N = 295, 71.9% transfers,
94.6% admitted to ICU,
79.7% with GCS = 15, mean GCS 14.5
Child abuse: Likely (8.6%), unclear (6%)
29/296 (9.7%) without a critical care intervention in the field or in the ED had a CCI after admission
#1 critical care intervention was neurosurgical intervention

	CRITICAL CARE INTERVENTION		
	YES	NO	
RULE (+)	28	104	132
RULE (-)	1	163	164
	29	267	296

PREDICTOR DEFINITION	ODDS RATIO (95% CI)
Midline shift on initial CT: (Yes)/(No)	6.90 (2.04, 23.28)
Skull fracture: (Depressed)/(Non-depressed or None)	9.49 (3.66, 24.58)
Mechanism: (Unknown) /(Mild or Moderate or Severe):	4.03 (1.43, 11.34)
Other injury: (Non-extremity injury)/(No other injuries, Extremity injury only)	1.97 (0.673, 5.77)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)
Sensitivity: 28/29 = 96.6%, 95% CI (82.2, 99.9%) Predictive Value (-) Rule: 163/164 = 99.4% (96.6, 99.9%) Likelihood Ratio (+) Rule: (28/29)/(104/267) = 2.479, 95% CI (2.068, 2.89)
HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Specificity and Predictive Value of a Positive Rule with 95% confidence intervals)
Specificity: 163/267 = 61.1%, 95% CI (54.9, 66.9%) Predictive Value (+) Rule: 28/132 = 21.2% (15.1, 28.9%) Likelihood ratio (-): Rule: (28/29)/163/267) = 0.056, 95% CI (-0.053, 0.166)
HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?
164/296 (55.4%) were considered negative by the rule and could potentially not be admitted to the ICU. Alternatively, 44.6% would be admitted to the ICU if the rule was followed. Since the rate of ICU admission in the study was 94.6% then 50 % (94.6% - 44.6%) of ICU admissions could potentially be avoided.
WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?
No. There was no internal statistical validation of the rule.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

At what level of development is this rule? How can it be applied? (see appendix)	☐ I ☐ II ☐ III ■ IV This is a level IV rule. A level IV rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. A level IV rule requires further validation before it can be applied clinically
Does the rule make clinical sense?	Yes. The four identified predictors make clinical sense
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. The predictor “absence of other non-extremity injuries” is somewhat subjective and would need to be clearly defined. In addition, CT readings were not interpreted by a second radiologist so that the reproducibility of the CT findings of midline shift and depressed skull fracture could not be assessed.
Is the rule applicable to the patients in my practice?	Unclear. 72% of patients were transfers possibly leading to referral bias. Transfer of patients requires some time so these patient have a longer observation period to determine the urgent need for a critical care intervention.
Will the rule results change my management strategy?	No. Not at present. The rule required further validation. Any change in management strategy would require collaboration with the intensivists, hospitalists, neurosurgeons and trauma surgeons.
What are the benefits of applying the rule to my patients?	Use of the rule could potentially decrease the ICU admission rate 50% from a baseline study rate of 95%. The authors estimate cost of an ICU stay at $ 7000 per day for room and board alone. This is roughly 3 to 5 times the cost of ward level care.
What are the risks of applying the rule to my patients?	The primary risk of applying the rule is admitting a patient to the floor that subsequently requires a critical care intervention. Patients may not be as closely monitored and a delay in intervention may occur. Only 1 patient (0.3% of all patients, 3.4% of those requiring an intervention) required a critical care intervention) would have been consider at low risk by the rule.

CLINICAL BOTTOM LINE

BACKGROUND: Traditionally, pediatric patients with traumatic brain injury are admitted to an intensive care unit for close monitoring to identify clinical deterioration and provide timely interventions. However, only a small percentage of these patients require a critical care intervention and if patients at low risk for requiring an intervention could be identified prospectively then an intensive care unit admission could be potentially avoided.

CLINICAL QUESTION: In pediatric patients with minor traumatic brain injury and intracranial hemorrhage and who do not require critical care intervention in the field or in the emergency department, can clinical and radiologic findings identify those at low risk for requiring a critical care intervention during their inpatient stay?

DESIGN/RISK OF BIAS: This was a well-designed retrospective cohort study that included 296 pediatric patients with traumatic intracranial hemorrhage. The aim of the study was to derive a clinical prediction rule that identifies patients at low risk for requiring a critical care intervention after admission and thus could potentially not require an intensive care unit admission. The primary validity concern is the potential lack of reproducibility of the rule parameters as this was not assessed. In addition, some of the predictors including two that are present in the final rule occurred infrequently, limiting the assessment of the significance of these characteristics.

PRIMARY RESULTS: 29/296 (9.7%) without a critical care intervention in the field or in the ED required a critical care intervention after admission. The number one critical care intervention was neurosurgical intervention (see Appendix for definitions). The rule identified 4 significant independent predictors of the need for a critical care intervention. The rule had a sensitivity of 96.6%, 95% CI (82.2, 99.9%), and a predictive value of a negative rule of 99.4%, 95% CI (96.6, 99.9%). The rule had a specificity of 61.1%, 95% CI (54.9, 66.9%) and a predictive value of a positive rule of 21.2%, 95% CI (15.1, 28.9%). Overall the rule divided a population with a 9.7% risk of requiring an intervention into a low risk group (0.6%) if all of the rule parameters were absent and a non-low risk group (21.2%) if any of the rule parameters were present. 55.4% were considered negative by the rule and could potentially not be admitted to the ICU.

RULE: LOW RISK CRITERIA
Known/Witnessed mechanism
Initial head CT without midline shift
Initial head CT without a depressed skull fracture
Absence of other non-extremity injuries

APPLICABILITY: The predictor “absence of other non-extremity injuries” is somewhat subjective and would need to be clearly defined. In addition, CT readings were not interpreted by a second radiologist so that the reproducibility of the CT findings of midline shift and depressed skull fracture could not be assessed. A prospective validation of the rule should include an assessment of the reproducibility of the rule criteria.

This is a level IV rule. A level IV rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods. A level IV rule requires further validation before it can be applied clinically.

AUTHOR'S CONCLUSION: "In conclusion, we were able to derive a Clinical decision instrument that accurately identified a subset of patients with traumatic intracranial hemorrhage who are at very low risk of requiring an acute critical care intervention, and this subset of patients likely does not warrant intensive care unit admission. If prospectively validated, adoption of a clinical decision rule such as ours could have a significant impact on the usage of limited resources."

POTENTIAL IMPACT: If validated this decision rule has the potential to significantly reduce intensive care unit admission for pediatric patients with traumatic intracranial hemorrhage. A prospective validation of the rule should include an assessment of the reproducibility of the rule criteria. A larger sample size could remedy the low prevalence of some of the rule predictors.There are other benefits of ICU care than just those limited to critical care interventions. There remains a low risk of patients requiring a critical care intervention who would not be identified by the rule. Any change in management strategy would require collaboration with the intensivists, hospitalists, neurosurgeons and trauma surgeons.

APPENDIX: STUDY DEFINITIONS

MECHANISM	
SEVERE	MVC with ejection, rollover, death of a passenger Un-helmeted pedestrian or bicyclist struck by vehicle Fall from height: > 1.5 meters if > 2 years, > 0.9 meters if < 2 years Head struck by high impact object
MODERATE	Any non-severe or non-mild with known mechanism
MILD	Ground level fall Walked or ran into a stationary object
UNKNOWN	Any unknown of unwitnessed mechanism

CRITICAL CARE INTERVENTIONS	
Assisted ventilation	Use of invasive or noninvasive positive pressure ventilation for acute respiratory failure; excluding perioperative mechanical ventilation
Hyperosmolar therapy	Use of hypertonic saline or mannitol for management of increased intracranial pressure
Vasoactive medication use	Use of dopamine, epinephrine, milrinone, dobutamine, norepinephrine, phenylephrine, or vasopressin for hemodynamic instability
Blood product transfusion	Transfusion or packed RBCs, FFP, platelets, or cryoprecipitate
Invasive monitoring	Use of central venous or arterial catheters to measure pressures invasively and continuously
Cardiopulmonary resuscitation, management of arrhythmia	Cardiac arrest requiring CPR or non-sinus arrhythmia with need for urgent intervention
Interventional angiography	Diagnostic or therapeutic angiography
Neurosurgical intervention	Including craniotomy/craniectomy, burr hole evacuation of hematoma, placement of subdural drain, placement of ICP monitoring device or intraventricular catheter

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

HEAD TRAUMA:
ICU ADMISSION DECISION RULE DERIVATION

In pediatric patients with severe traumatic brain injury, does hyperosmolar therapy with Hypertonic Saline or Mannitol reduce intracranial pressure and improve clinical outcomes?

Michael Mojica, MD
October 2019

Stopa BM, Dolmans RGF, Broekman MLD, Gormley WB, Mannix R, Izzy S.

HYPEROSMOLAR THERAPY IN PEDIATRIC SEVERE TRAUMATIC BRAIN INJURY: A SYSTEMATIC REVIEW.

Crit Care Med. 2019 Sep 25 [Epub ahead of print]
PubMed ID: 31567404

STUDY DEFINITIONS	
POPULATION	Patients Inclusion: < 18 years, severe traumatic brain injury Exclusion: Mild to moderate traumatic brain injury (GCS > 8) Studies Inclusion: Randomized clinical trials, retrospective and prospective cohort Exclusion: Non-English, case series, adult studies or adult/pediatric studies for which the data could not be separated by age, full text not available, intended outcomes not linked to hyperosmolar therapy, animal studies, review articles and abstracts
INTERVENTION	Hypertonic Saline: 1.7%, 3%, 23.4% (bolus or infusion), varying dosages
CONTROL	Mannitol (20%): 0.5-1.0 mg/kg (bolus or infusion)
OUTCOME	Physiologic*: ICP, CPP, MAP, CVP, Serum osmolarity Clinical*: Days on ventilation Need for surgical intervention Number of complications Number of interventions/doses Length of stay: ICU, Hospital Functional status score at hospital discharge Mortality: In-hospital, 6 months, 12 months GOS (Glasgow Outcome Scale): 6 months, 3-12 months Extended GOS: 6 months *Study outcomes were disparate
DESIGN	Systematic Review of RCT and cohort studies

HOW SERIOUS WAS THE RISK OF BIAS?	
Did the review explicitly address a sensible clinical question?	Yes. The study question was sensible but the available evidence did not frequently address the specific question asked. 4 of 11 studies compared 3% Saline to Mannitol. 1 of the 4 studies was a randomized clinical trial. Studies differed in inclusion criteria, interventions, controls, outcomes and study design.
Was the search for relevant studies detailed and exhaustive?	Yes. The authors searched PubMed, Embase and Cochrane until 5/2019. Search criteria are presented in the appendix. In addition, the citations of identified articles were searched. Non-English articles were excluded. There was no assessment of the likelihood of publication bias.
Was the risk of bias of the primary studies assessed?	Yes, Study quality was assessed with the Oxford Quality Scoring System for randomized clinical trials and the Newcastle-Ottawa Scale for cohort studies. Study quality was poor. Only one of the 11 identified studies would meet criteria for inclusion in the next guideline. 2 of the 3 randomized clinical trials were assessed as low quality. 7 of the 8 cohort studies were assessed as poor quality.
Were the selection and assessment of studies reproducible?	No. Inter-rater reliability was not assessed for study inclusion and quality.

WHAT WERE THE RESULTS?

WERE THE RESULTS SIMILAR FROM STUDY TO STUDY?

N = 11 studies (358 patients)
RCT (3), Prospective cohort (2), Retrospective cohort (6)
4 studies compared 3% Saline to Mannitol (RCT (1), retrospective cohort (2), prospective cohort(1))
9 of the 11 studies assessing hypertonic saline demonstrated a significant decrease in ICP
2 of the 4 studies assessing Mannitol demonstrated a significant decrease in ICP

The results of the single randomized trial comparing 3% saline to Mannitol are summarize in the table below. This study was published after completion of the 2019 pediatric guidelines. It is the only study in the systematic review that would meet current level of evidence criteria for the guidelines. Of note, the study assessed the efficacy of hypertonic saline and mannitol for increased intracranial pressure that was refractory to therapeutic CSF drainage.

PHYSIOLOGY AND CLINICAL OUTCOMES

	3% HTS (n=14)	20% MANNITOL (n=16)
▲ICP (mmHg)	↓ 5.67	↓ 7.13
▲CPP (mmHg)	↑ 6.48	↑ 5.89
Refractory ICP (#)	1.21	1.13
Ventilation (days)	8.64	8.18
LOS ICU (days)	9.64	9.5
LOS Hospital (days)	11.7	14.2
Survival (6 months)	86%	81%
Kumar, Childs Nerv System 2019, PubMed ID: 30879126		

WHAT ARE THE OVERALL RESULTS OF THE REVIEW?

A meta-analysis was not completed. Evidence supports the use of hypertonic saline and Mannitol to decrease intracranial pressure but evidence on improvement in clinical outcomes is less clear. There is insufficient evidence to recommend one form of hyperosmolar therapy over the other.

DID THE REVIEW ADDRESS CONFIDENCE IN EFFECT ESTIMATES?

No. This was a systemic review that did not include a meta-analysis. The results are descriptive. A summary statistic with a confidence interval was not provided.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	No. These were primarily ICU patients with CSF drains. It is unclear if the data presented can be generalized to patients initially managed in the ED.
Was follow-up complete and sufficiently long?	Unclear. Longs term outcomes varied and data was not complete. Authors used an outcome of survival to hospital discharge as a surrogate measure.
Is the exposure similar to what might occur in my patient?	Yes. Hyperosmolar therapy for increased intracranial pressure is used frequently for pediatric patients with severe traumatic brain injury.
What is the magnitude of the risk?	Unclear. A meta-analysis was not performed. The single RCT comparing 3% saline to Mannitol did not demonstrate a difference in physiologic and clinical outcomes between the two therapies.
Are there any benefits that offset the risks associated with exposure?	Theoretical benefits of hyperosmolar therapy include a decrease in ICP and a subsequent decrease in the risk of herniation.

CLINICAL BOTTOM LINE

BACKGROUND: Hyperosmolar therapy is frequently used to lower intracranial pressure in patients with severe traumatic brain injury. However, the evidence to support its use is limited. This is particularly true for pediatric patients.

The brain trauma foundation adult guidelines (Neurosurgery 2017, PubMed ID: 27654000) state that "Although hyperosmolar therapy may lower intracranial pressure, there was insufficient evidence about effects on clinical outcomes to support a specific recommendation, or to support use of any specific hyperosmolar agent, for patients with severe traumatic brain injury." The brain trauma foundation pediatric guidelines allow for use of bolus 3% Saline (Level II evidence), as an infusion (Level III evidence) and 23.4% Saline for refractory increase intracranial pressure (Pediatr Crit Care Med, 2019, PubMed ID: 30829890). The pediatric guidelines draw the following conclusions regarding Mannitol. "Although mannitol is commonly used in the management of raised ICP in pediatric TBI, no studies meeting inclusion criteria were identified for use as evidence for this topic. "Mannitol has not been subjected to contemporary controlled clinical trials versus placebo, other osmolar agents, or other therapies in children.

The aim of this study was "to evaluate the evidence supporting these two hyperosmolar therapies [mannitol and hypertonic saline] to better understand which may produce better clinical outcomes in pediatric severe TBI patients."

CLINICAL QUESTION: In pediatric patients with severe traumatic brain injury, does hyperosmolar therapy with Hypertonic Saline or Mannitol reduce intracranial pressure and improve clinical outcomes?

DESIGN/RISK OF BIAS: This was a systemic review of 11 studies including 358 pediatric patients with severe traumatic brain injury. Studies differed in inclusion criteria, interventions, controls, outcomes and study design. These differences precluded a meta-analysis. Non-English articles were excluded and there was no assessment for publication bias. In addition, inter-rater reliability for study inclusion and quality was not assessed.

Study quality was assessed with the Oxford Quality Scoring System for randomized clinical trials and the Newcastle-Ottawa Scale for cohort studies. Study quality was poor. 2 of the 3 randomized clinical trials were assessed as low quality and 7 of the 8 cohort studies were assessed as poor quality.

4 of the 11 studies directly compared 3% Saline to Mannitol. Only 1 of these 4 studies was a randomized clinical trial including 30 patients. This RCT was the only study that would meet quality criteria for inclusion in the next guideline.

PRIMARY RESULTS: Evidence supports the use of hypertonic saline and Mannitol to decrease intracranial pressure. 9 of the 11 studies assessing hypertonic saline demonstrated a significant decrease in ICP. 2 of the 4 studies assessing Mannitol demonstrated a significant decrease in ICP. Evidence of improvement on clinical outcomes is less clear. There is insufficient evidence to recommend one form of hyperosmolar therapy over the other in the normotensive patient.

The results of the single randomized trial comparing 3% saline to Mannitol are summarize in the table below. This was not available for inclusion in the 2019 pediatric guidelines. Of those, this study assessed the efficacy of hyperosmolar therapy for increase intracranial pressure only in those refractory to therapeutic CSF drainage.

PHYSIOLOGY AND CLINICAL OUTCOMES		
	3% HTS (n=14)	20% MANNITOL (n=16)
▲ICP (mmHg)	↓ 5.67	↓ 7.13
▲CPP (mmHg)	↑ 6.48	↑ 5.89
Refractory ICP (#)	1.21	1.13
Ventilation (days)	8.64	8.18
LOS ICU (days)	9.64	9.5
LOS Hospital (days)	11.7	14.2
Survival (6 months)	86%	81%
Kumar, Childs Nerv System 2019, PubMed ID: 30879126		

APPLICABILITY: These were primarily ICU patients with CSF drains. It is unclear if the data presented can be generalized to patients managed in the ED. In addition, the single randomized trial assessed the efficacy of 3% saline and Mannitol for increased intracranial pressure that was refractory to therapeutic CSF drainage. This would not be an option in the ED.

AUTHOR'S CONCLUSION: "Both HTS and mannitol appear to lower ICP and improve clinical outcomes in severe TBI, but the evidence is extremely fractured both in the method of treatment and in the evaluation of outcomes. There is more evidence to support the use of HTS in pediatric severe TBI. Given the limited high-quality data relating to the use of HTL versus mannitol in pediatric severe TBI, it is difficult to draw definitive conclusions about which agent is superior or about the treatment protocol to follow. Despite the current clinical preference for management with HTS, the data does not show clear superiority for one treatment over another. In order to determine scientifically the better therapy, a large-scale prospective comparative effectiveness study is needed."

POTENTIAL IMPACT: This study primarily serves to highlight the poor level of evidence to support the use of hyperosmolar therapy in pediatric patients with severe traumatic brain injury. Unfortunately, this is true of adults as well as reflected by the 2017 adult guidelines.

It appears that both hypertonic saline and Mannitol reduce intracranial pressure but the impact on clinical outcomes is less clear. Mannitol is a potent diuretic and 2018 ATLS guidelines recommend to avoid it's use in the hypotensive patient. The ADAPT (Approaches and Decisions in Acute Pediatric TBI) trial is a planned, multicenter, prospective cohort study intending to include 1,000 pediatric patients with severe traumatic brain injury that will hopefully provide a higher level of evidence on this topic.

See Also:
Kumar SA, Devi BI, Reddy M, Shukla D.
Comparison of Equiosmolar Dose of Hyperosmolar Agents in Reducing Intracranial Pressure: A Randomized Control Study in Pediatric Traumatic Brain Injury.
Childs Nerv Syst. 2019 Jun;35(6):999-1005., Epub 2019 Mar 16., PubMed ID: 30879126

HEAD TRAUMA:
ICU ADMISSION DECISION RULE (PECARN)

In pediatric patients with mild traumatic brain injury and intracranial injury on CT scan, do clinical and imaging findings accurately identify those requiring neurosurgical intervention or intubation for greater than 24 hours?

Michael Mojica, M.D.
June 2018

Greenberg JK, Yan Y, Carpenter CR, Lumba-Brown A, Keller MS, Pineda JA, Brownson RC, Limbrick DD.

DEVELOPMENT AND INTERNAL VALIDATION OF A CLINICAL RISK SCORE FOR TREATING CHILDREN WITH MILD HEAD TRAUMA AND INTRACRANIAL INJURY

JAMA Pediatr. 2017 Apr 1;171(4):342-349.
PubMed ID: 28192567

STUDY DEFINITIONS	
POPULATION	Inclusion: < 18 years, blunt heads trauma, ED CT indicating intracranial injury including: intracranial hemorrhage, cerebral edema, skull diastasis, midline shift, pneuomocephalus, depressed skull fracture (≥ width of the skull), traumatic infarction, diffuse axonal injury, herniation, shear injury, sigmoid sinus thrombosis. Exclusion: Trivial mechanism: Fall from ground level, walk, run into stationary object with no signs or symptoms other than scalp abrasions and lacerations History: Central nervous system tumor, preexisting neurologic disease, penetrating trauma, bleeding disorders, neuroimaging prior to presentation. Setting: 25 Children's Hospital EDs in the PECARN network. Derivation set: 6/2004-3/2006, Validation set: 3/2006-9/2006
RULE PARAMETERS	Standardized data collection process including 19 clinical variables (assessed prior to imaging) and 18 radiologic variables extracted from radiology reports (see supplement online).
REFERENCE STANDARD	Composite outcome of: 1. Neurosurgical intervention 2. Intubation for > 24 hours for traumatic brain injury 3. Death Separately assessed for admission for > 48 hours which was the 4th component of the definition of clinically important traumatic brain injury in the parent study
OUTCOME	Rule Characteristics at identified score cutoffs Model score: Area under the receiver operating characteristic curve
DESIGN	Observational: Prospective cohort (Secondary analysis of the PECARN head trauma derivation/validation study)

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. Standardized data collection process including 19 clinical variables (assessed prior to imaging) and 18 radiologic variables extracted from radiology reports (see supplement online).
Were all important predictors present in significant proportion of the study population?	Unclear. Table 1 list the clinical and CT findings in patients with and without the composite outcome. Approximately 13% of patient had a GCS of 13 and was one of the rule predictors. Cerebral edema was a rare CT finding.
Were the outcome event and predictors clearly defined?	Yes. The composite outcome of 1. Death, 2. Neurosurgical intervention (ICP monitor placed or hematoma evacuation) and 3. Intubation for > 24 hours were clearly defined. Predictors were also objective. All except scalp hematoma had a kappa statistic > 0.5 which is considered moderate.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Unclear. The was a retrospective analysis of a prospectively collected dataset. Clinical predictors were recorded prior to the results of imaging. It is unclear if radiologist received clinical data prior to their interpretation of the CT scan. CT scan reports were utilized in this study and inter-rater reliability for CT interpretation was not provided. Knowledge of the CT findings were certainly the basis of the decision for neurologic intervention and likely for intubation for greater than 24 hours.
Was the sample size adequate (including an adequate number of outcome events)?	Yes. In general, 10 outcomes are required for each variable in multiple logistic regression. The study included 73 patients with intracranial injury on CT who met the study's outcome definition and rule included 5 variables (15 outcomes per rule variable)

WHAT ARE THE RESULTS?

N = 839 with TBI Non-depressed skull fracture (43.1%) Contusion/intraparenchymal hematoma (24.7%) Subdural hematoma (24.7%) Age: 65.4% > 2 years GCS: 72.8% with GCS I5	<u>Outcomes (n=73/839) (8.7%))</u> Neurosurgical intervention: 70 (8.3%) Intubated > 24 hours for TBI: 11(1.3%) Death: 0 (0%) (Admit for > 48 hours: 50.2%)
How well did the rule correctly identify patients <u>with</u> the primary outcome? How precise was this measurement? How well did the rule correctly identify patients <u>without</u> the primary outcome? How precise was this measurement?	

Logistic regression analysis: 2 clinical variables and 3 radiologic variables were found to be independent predictors of the study outcome
Model c-statistic: 0.83, 95% CI (0.79, 0.78)
Calibration in the large statistic: -0.08 (low overprediction or underprediction)
Calibration slope: 0.95 (close agreement between predicted and observed)
R^2 Coefficient of Determination: 40% (40% of ED disposition predicted by rule)

CHILDREN'S INTRACRANIAL INJURY DECISION AID RISK (CHILDA) SCORE

VARIABLE	ODDS RATIO (95% CI)	BETA	POINTS
Depressed Skull Fracture	6.5 (3.7, 11.4)	1.9	7
Midline Shift	6.8 (3.4, 13.8)	1.9	7
Epidural Hematoma	3.4 (1.8, 6.2)	1.2	5
GCS 13	1.6 (0.82, 3.1)	0.46	5
GCS 14	3.4 (1.5, 7.4)	1.2	2
Score Range: 0-24 points			

SCORE TEST CHARACTERISTICS

	ICU Admit for SCORE > 0	ICU Admit for SCORE > 2
Sensitivity	93.2% (84.7, 97.7%)	86.3% (76.3, 93.2%)
Specificity	55.5% (51.9, 59.0%)	70.4% (67.0, 73.6%)
Predictive Value Positive	16.6% (13.2, 20.6%)	21.7% (17.1, 26.9%)
Predictive Value Negative	98.8% (97.3, 99.6%)	98.2% (96.7, 99.1%)
Avoid ICU admission	51.3%	65.4%

How would use of the rule impact resource utilization?	Using a score of > 0 for ICU admission, 51.3% could have potentially avoided ICU admission. Using a score of > 2 for ICU admission, 65.4% could have potentially avoided ICU admission.
Was there an internal statistical validation of the results? How did it compare to the primary results?	Yes. Internal validation using 10-fold cross validation was completed. The validation c statistic was 0.85, 95% CI (0.79. 0.88) (Note: A perfect c statistic is 1.0)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (See appendix)	☐ I ☐ II ☐ III ■ IV The rules meet level IV criteria. The rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods". The rule requires further validation before it can be applied clinically
Does the rule make clinical sense?	Yes. The rules do make clinical sense. Rule parameters are factors we typically consider defining risk of intervention for intracranial injury.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Unclear. All of the clinical parameters evaluated had a kappa of > 0.5 indicating a moderate degree of inter-rater reliability. Inter-rater reliability for radiology predictors were not assessed.
Is the rule applicable to the patients in my practice?	Yes. This study included ED patients at multiple sites throughout the U.S. Applicability to non- children's hospital settings is unclear.
Will the rule results change my management strategy?	The impact of the rule on management strategy will depend on the current approach to disposition in patients with intracranial injury on CT and would require collaboration with hospitalists, intensivists, trauma surgery and neurosurgery
What are the benefits of applying the rule to my patients?	The rules would identify almost all the patients with intracranial injury on CT with one of the study outcomes and may decrease the rate of ICU admission.
What are the risks of applying the rule to my patients?	Confidence intervals include the rare possibility of missing patients with intracranial injury that requires an intervention. 1.2% of patients with a score of 0 required an intervention. 1.8% of patients with a score of less than required an intervention.

CLINICAL BOTTOM LINE

BACKGROUND: Intracranial injury on CT after blunt head trauma occurs in approximately 5% of pediatric patients with a Glasgow Coma Scale of greater than 14. The majority of patients with CT findings do not require intervention but may benefit from close observation in a monitored setting. Traditionally, these patients have been admitted to a pediatric intensive care unit. This study is a secondary analysis of the derivation and validation data set of the PECARN head trauma rule (PECARN, Lancet 2009, PubMed ID: 19758692). The goal of this study was to "use prospective, multicenter data to develop a generalizable clinical decision tool to risk stratify the need for ICU admission among children with complicated mild traumatic brain injury".

CLINICAL QUESTION: In pediatric patients with mild traumatic brain injury and intracranial injury on CT scan do clinical and imaging findings accurately identify those requiring neurosurgical intervention or intubation for greater than 24 hours?

DESIGN/VALIDITY: This was a well design prospect cohort study that is a secondary analysis of the PECARN head trauma rule data set. Standardized data collection process included 19 clinical variables (assessed prior to imaging) and 18 radiologic variables extracted from radiology reports. Multivariable logistic regression was used to identified independent predictors of the composite outcome of: 1. Neurosurgical intervention, 2. Intubation for greater than 24 hours for traumatic brain injury, 3. Death.

PRIMARY RESULTS: The study included 839 patients with traumatic brain injury on CT scan. The majority of patients were older than two years of age (65.4%) and had a Glasgow Coma Scale of 15 (72.8%). The most common intracranial injuries were: non-depressed skull fracture (43.1%), contusion/ intraparenchymal hematoma (24.7%) and subdural hematoma (24.7%). 8.7% (73/839) required a study intervention (neurosurgical intervention: 70 (8.3%), intubated > 24 hours for TBI: 11(1.3%), death: 0 (0%).

Logistic regression analysis identified 2 clinical variables and 3 radiologic variables that were independent predictors of the study outcome. A CHILDA score stratified children with a baseline 8.7% risk of requiring a study intervention into a high risk group (16.6%) if the score was greater than zero and a low risk group (1.2%) if the score was equal to 0. Using a score of greater than 0 for ICU admission, 51.3% could have potentially avoided ICU admission. A CHILDA score stratified children with a baseline 8.7% risk of requiring a study intervention into a high risk group (21.7%) if the score was greater than two and a low risk group (1.8%) if the score was less than or equal to 2. Using a score of greater than 2 for ICU admission, 65.4% could have potentially avoided ICU admission.

CHILDREN'S INTRACRANIAL INJURY DECISION AID RISK (CHILDA) SCORE	
VARIABLE	POINTS
Depressed Skull Fracture	7
Midline Shift	7
Epidural Hematoma	5
GCS 13	5
GCS 14	2
Score Range: 0-24 points	

CHILDA SCORE: TEST CHARACTERISTICS		
	ICU Admit for SCORE > 0	ICU Admit for SCORE > 2
Sensitivity	93.2% (84.7, 97.7%)	86.3% (76.3, 93.2%)
Specificity	55.5% (51.9, 59.0%)	70.4% (67.0, 73.6%)
Predictive Value Positive	16.6% (13.2, 20.6%)	21.7% (17.1, 26.9%)
Predictive Value Negative	98.8% (97.3, 99.6%)	98.2% (96.7, 99.1%)
Avoid ICU admission	51.3%	65.4%

APPLICABILITY: The rule appears sensible and easy to apply. The study included 25 children's hospital EDs and is therefore likely generalizable to patients meeting the study's inclusion and exclusion criteria in that setting. The applicability to non-ED settings is less clear. The radiologic variables appear objective though inter-rater reliability on these finding was not assessed because only imaging reports and not actual images were available.

The rules meet level IV criteria (See appendix). The rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods". The rule requires further validation before it can be applied clinically

AUTHOR'S CONCLUSION: "Using data from a large, prospectively collected, multicenter data set, we found that lower Glasgow Coma score, midline shift, depressed skull fracture, and epidural hematoma are independent predictors of needing ICU-level care in children with complicated mild traumatic brain injury. These factors served as the basis for developing the Children's Intracranial Injury Decision Aid Risk (CHILDA) score, a decision tool to aid physicians treating these patients."

POTENTIAL IMPACT: This decision rule has the potential to significantly reduce intensive care unit admission for pediatric patients with traumatic intracranial hemorrhage. The authors recommend that "nearly all children with 0 points and many children with less than 3 points be admitted to a general ward. In contrast, patients at higher risk levels should likely be admitted to an ICU or higher-acuity stepdown unit in most circumstances". There remains a low risk of patients requiring an intervention who would not be identified by the rule. The rule requires further validation. Any change in management strategy would require collaboration with the intensivists, hospitalists, neurosurgeons and trauma surgeons.

APPENDIX: DEVELOPMENT AND APPLICABILITY OF CLINICAL DECISION RULES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

HEAD TRAUMA:
ISOLATED SCALP HEMATOMA (PECARN)

In children < 24 months of age with an isolated scalp hematoma after sustaining non-trivial blunt head trauma, is patient age, size and location of the hematoma and mechanism of injury accurate in identifying those with and without traumatic brain injury on head CT and clinically important traumatic brain injury (ciTBI)?

Joshua Beiner, M.D., Susan Torrey, M.D.
April 2014

Dayan PS, Holmes JF, Schutzman S, Schunk J, Lichenstein R, Foerster LA, Hoyle J Jr, Atabaki S, Miskin M, Wisner D, Zuspan S, Kuppermann N; Traumatic Brain Injury Study Group of the Pediatric Emergency Care Applied Research Network (PECARN)

RISK OF TRAUMATIC BRAIN INJURIES IN CHILDREN YOUNGER THAN 24 MONTHS WITH ISOLATED SCALP HEMATOMAS.

Ann Emerg Med. 2014 Aug;64(2):153-62.
PubMed ID: 24635991

STUDY DEFINITIONS	
POPULATION	Inclusion: < 24 months, GCS 15, isolated scalp hematoma meeting criteria for the Extensive definition or PECARN definition (See Appendix). Patients with trauma to other body regions or those who were possibly physically abused were not excluded Exclusion: Patients with trivial head trauma mechanisms (i.e., ground-level falls or running into stationary objects) and either no signs of head trauma on exam or only scalp lacerations/abrasions. Also excluded were those with penetrating trauma, know brain tumors, pre-existing neurologic disorders than would complicate assessment, ventricular shunts, bleeding disorders, previous neuroimaging. Setting: 25 Pediatric EDs (PECARN network). 6/2004-9/2006.
PARAMETERS	Standardized data collection process completed prior to results of imaging: Mechanism (13 factors), History (7 factors), Physical (9 factors), Other (5 factors). Isolated scalp hematoma: Age, hematoma location, size, mechanism of injury Age: 0-3 months, 3-6 months, 6-12 months, 12-24 months Location: Frontal parietal, temporal, occipital. (if > 1, priority to site with highest risk: Temporal > Parietal > Occipital > Frontal) Size: Small < 1 cm or barely palpable, moderate 1-3cm, large > 3 cm Mechanism: Mild: Ground-level falls or running into stationary objects Moderate: Any mechanism not meeting mild or severe definitions Severe: Motor vehicle crash with patient ejection, death of another passenger, or rollover; pedestrian or bicyclist without helmet struck by a motorized vehicle, falls 3 feet or greater, or head struck by a high-impact object.
REFERENCE STANDARD	1. CT at MD discretion interpreted by site faculty radiologists or study radiologist if inconclusive 2. Clinical follow-up of discharged patients. Standardized telephone surveys 7-90 days post ED visit, evaluation of city medical examiner records if unavailable 3. Hospital course for admitted patients Traumatic Brain Injury (TBI): Intracranial hemorrhage or contusion, cerebral edema traumatic infarction, diffusive axonal injury, shearing injury, signs of brain herniation, diastasis of the skull, pneumocephalus or depressed skull fracture Clinically Important Traumatic Brain Injury (ciTBI): TBI above associated with: 1. Death 2. Neurosurgical intervention 3. Intubation for > 24 hours 4. Admission for > 48 hours for persistent signs or symptoms of head trauma
OUTCOME	Test characteristics for age, hematoma location, size and mechanism of injury Rate of TBI and ciTBI Association of TBI and ciTBI with age, hematoma location, size and mechanism of injury (Regression analysis not performed for ciTBI due to too few outcomes
DESIGN	Observational: Prospective cohort study (Planned secondary analysis)

ARE THE RESULTS VALID?	
Were all important predictors included in the derivation process?	Yes. All feasible important predictors were included. Headache and amnesia were intentionally left out due to the study population's age. "Victim of non-accidental trauma" was not explicitly included, however, "Assault" was included, and details of abuse were described in an "Other" category. The 2 definitions of isolated skull hematoma varied slightly, and all included patients met the "Extensive" definition. The "Extensive" version excluded patients with vomiting, seizure activity, focal neurologic deficits, and signs of basilar fracture. Although all primary analysis PECARN information was collected, patients were not excluded for "Severe Mechanism of Injury" or "Non-frontal Scalp Hematoma" as these predictors are the focus of this analysis.
Were all important predictors present in significant proportion of the study population?	Yes. Patients who did not meet the "Extensive" definition were excluded so that only patient age, mechanism of injury, and hematoma characteristics were analyzed. Since only the 19% (N=570) with Head CTs can be assessed for both outcomes, this subgroup should be representative of the larger patient population. However, CTs were ordered at the discretion of the faculty/fellow physician, and CTs were ordered more often in patients < 3 months, with temporal/parietal hematomas, and with large (>3 cm) hematomas (Table 2). There are no p-values to denote between-group differences in those "With Head CT vs Without" (Table 2), or those imaged by "CT versus Skull Radiographs" (Table 3).
Were the outcome event and predictors clearly defined?	Yes. Predictors, including age in months, hematoma location, hematoma size, and mechanism of injury severity, were defined in the "Methods of Measurement" section. Clinically important traumatic brain injury was defined as death from traumatic brain injury, neurosurgical intervention, intubation for ≥ 24 hours or hospitalization ≥ 2 nights secondary traumatic brain injury.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Unclear. Faculty/fellow physicians completed standardized data forms prior to determination of need for imaging and prior to disposition. Head CTs were read by faculty radiologists at each site, and it is not specified whether or not radiologists received clinical patient information. Equivocal CT findings were interpreted by the study radiologist who was blinded to the previous interpretation. It is unlikely, though, that clinical information provided to the radiologist would bias the interpretation. ciTBI outcome was determined by a blinded review medical records for admitted patients, and by follow-up telephone calls or mail surveys, quality improvement logs, trauma registries, and morgue logs for those discharged.
Was the sample size adequate (including an adequate number of outcome events)?	Target numbers of patients/outcome-events or power analysis were not reported. Multivariate logistic regression was used to find association between proposed predictors and the outcome of traumatic brain injury on Head CT. A regression analysis was not performed for ciTBI outcome because there were too few of these outcomes (0.4%).

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? How precise was this measurement? (Sensitivity and Predictive Value of a Negative Rule with 95% confidence intervals)

N = 2,998 with isolated scalp hematoma (Extensive Definition)
CT rate: 19% (n=570)
TBI on CT: 1.7% (50/2,988)
ciTBI: 0.4% (12/2,988), 95% CI (0.2, 0.7%)
Admit for < 2 nights (12), Death (0), Neurosurgery (0), Intubation (0)

REGRESSION ANALYSIS: INDEPENDENT PREDICTORS OF TBI ON CT (TABLE 7)

PREDICTOR: CATEGORY/REFERENCE CATEGORY	ADJUSTED ODDS RATIO (95% CI)
Age: 0-3 month/12-24 month	17.0 (3.7, 78.5)
Age: 3-6 month/12-24 month	6.6 (1.4, 31.7)
Age: 6-12 month/12-24 month	3.6 (0.8, 17.0)
Location: Occipital/Frontal	3.3 (1.1, 10.1)
Location: Temporal/Parietal)/Frontal	4.5 (1.9, 10.8)
Size: Small/Medium	0.5 (0.1, 1.5)
Size: Large/Medium	3.3 (1.6, 6.8)
Mechanism: Severe/(Mild/Moderate)	2.4 (1.2, 4.7)

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

Using the proposed recommendations from the discussion section would likely increase CT utilization in infants < 3 months (regardless of hematoma size/location) and those with large hematomas. Non-frontal location and severe mechanism of injury were already independent risk-factors for ciTBI from the parent PECARN study, and when paired with young age and/or large hematoma size, this increased likelihood of traumatic brain injury on Head CT. Therefore, CT utilization would increase when these risks co-occur. CT use would likely decrease in those patients older than 3 months with small hematomas.

WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?

No. Validation on this subgroup of the patients was not performed. However, an inter-observer agreement analysis was conducted on a convenience sample of 4% of the parent study with Kappa of 0.87 for hematoma location, 0.74 for size and 0.88 for mechanism of injury in those < 24 months.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see appendix)	☐ I ☐ II ☐ III ☐ IV This was not a derivation of a clinical decision rule. It is a sub-analysis of the Stage II parent head trauma rule. Independent predictors of TBI on CT were identified but the predictors were not assembled into a decision rule.
Does the rule make clinical sense?	Yes. It makes sense that younger age, severe mechanism of injury, larger hematoma size, and non-frontal location are associated with signs of TBI on head CT.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	In the parent study, there was excellent inter-rater reliability of scalp hematoma location (kappa 0.87) and hematoma size (kappa 0.74), and mechanism of injury (kappa 0.88 in those younger than 2 years),
Is the rule applicable to the patients in my practice?	Yes. Minor blunt head trauma is a common presenting problem in the pediatric ED and isolated scalp hematoma is a common finding. The decision to image such patients is a frequently encountered dilemma.
What are the benefits of applying the rule to my patients?	Decreased use of head CT in certain low-risk patients. Using CT in certain subgroups may pick up CT findings that may not have been recognized. For example, in the parent study, of 4,713 patients with scalp hematomas, 820 had non-frontal hematoma without additional PECARN risk factors so CT imaging would be optional but not necessarily advised. Of this group, 4/820 (0.5%, 95% CI 0.1-1.2%) had ciTBI but 22/234 (9.4%, 95% CI 6.0-13.9%) had TBI on CT. Practitioners and families would likely want to be aware of injuries such as cerebral edema, diastasis of skull, or significantly depressed skull fracture even if intervention is not required immediately. These cases may warrant closer outpatient follow-up, extra developmental services, repeat imaging in the subacute period, etc.
What are the risks of applying the rule to my patients?	Head CT use will increase in certain subgroups of patients, especially in the youngest infants where the risks of ionizing radiation are also the highest. Findings on CT that do not require intervention may prompt further follow-up imaging that only increases the radiation burden. The recommendations may decrease radiation in older infants/toddlers with smaller or non-frontal hematomas from non-severe mechanisms. The greatest application of the recommendations will be to stratify those with isolated scalp hematomas into those to be observed as opposed to those who should have a CT.

CLINICAL BOTTOM LINE

BACKGROUND: Pediatric head trauma is a frequent presenting complaint and traumatic brain injury (TBI) is a common cause of pediatric morbidity and mortality. Those with GCS of 14-15 are the most frequently encountered in the ED and represent 40-60% of those who are imaged, but less than 10% have head CTs indicative of TBI and even fewer require a neurosurgical intervention.

The parent PECARN study (PECARN: Lancet 2009 PubMed ID: 19758692) identified 6 risk factors in those less than 24 months for clinically important traumatic brain injury (ciTBI) with a ciTBI rate of less than 0.02% (1 in 5,000) when all 6 variables were absent. The decision rule becomes less clear when 1 or more of the 4 lower-risk predictors is present. This occurred in 32.6% of the population that had a ciTBI rate of 0.9%. The provider is given an option in with these patients to CT or observe the patient. The aim of the study was to determine if factors such as: patient age, hematoma size and location, and mechanism of injury severity can be used to further risk stratify these patients.

CLINICAL QUESTION: In children < 24 months of age with an isolated scalp hematoma after sustaining non-trivial blunt head trauma, is patient age, size and location of the hematoma and mechanism of injury accurate in identifying those with and without traumatic brain injury on head CT and clinically important traumatic brain injury (ciTBI)?

DESIGN/VALIDITY: This study was a retrospective secondary analysis using data from a prospective observational parent cohort of pediatric hospitals in the PECARN network. The 2 primary outcomes were clinically important traumatic brain injury (ciTBI) and traumatic brain injury (TBI) on head CT. TBI on head CT could only be assessed in the subset of patients who had CTs (19%) ordered at the discretion of the physician. Notably, significantly more head CTs were ordered in patients' younger than < 3 months, those with larger hematomas, and with severe mechanisms of injury. This selection bias, could overestimate the prevalence of the outcomes in these groups. Unfortunately, there were too few patients with clinically important TBI (n=12) to complete a regression analysis on this outcome.

PRIMARY RESULTS: 2,998 with isolated scalp hematoma (Extensive Definition) were included. 19% (570/2,988) had a CT. Traumatic brain injury on CT was identified in 1.7% (50/2,988) of all patients with an isolated scalp hematoma and 8.8% (50/570) of those who had a CT. Clinically important TBI was identified in 0.4% (12/2,988), 95% CI (0.2, 0.7%). All ciTBI patients (n=12) met ciTBI criteria by admission for great than 2 nights. There were no patients with an isolated scalp hematoma who: died, required a neurosurgical intervention or intubation.

The regression analysis identified independent predictors of TBI on CT. These included: age < 3 months (Adjusted OR: 17.0, 95% CI (3.7, 78.5), age 3-6 months (Adjusted OR: 6.6, 95% CI (1.4, 31.7)), a non-frontal scalp hematoma (Occipital: Adjusted OR 3.3, 95% CI (1.1, 10.1), Temporal or Parietal: Adjusted OR: 4.5, 95% CI (1.9, 10.8)) and a severe mechanism (Adjusted OR: 2.4, 95% CI (1.2, 4.7)). Use of these predictors may increase the CT rate.

PREVALANCE: SCALP HEMATOMA + 1 OTHER RISK FACTOR		
	ciTBI	TBI on CT
Isolated non-frontal scalp hematoma	0.5% (0.1, 1.2%)	9.4% (6.0, 13.9%)
+ Altered mental status	2.2% (0.1, 11.8%)	17.6% (6.8, 34.5%)
+ LOC ≥ 5 seconds	0% (0, 20.6%)	7.1% (0.2, 33.9%)
+ Palpable skull fracture	1.4% (0, 7.5%)	28.3% (16.8, 42.3%)
+ Not acting normally per parents	1.7% (0, 9.1%	20.7% (8.0, 39.7%)
+ Severe mechanism of injury	3.0% (1.2, 6.1%)	21.2% (14.2, 29.7%)

REGRESSION ANALYSIS: INDEPENDENT PREDICTORS OF TBI ON CT (TABLE 7)	
PREDICTOR: CATEGORY/REFERENCE CATEGORY	ADJUSTED ODDS RATIO (95% CI)
Age: 0-3 months/12-24 months	17.0 (3.7, 78.5)
Age: 3-6 months/12-24 months	6.6 (1.4, 31.7)
Age: 6-12 months/12-24 months	3.6 (0.8, 17.0)
Location: Occipital/Frontal	3.3 (1.1, 10.1)
Location: (Temporal/Parietal)/Frontal	4.5 (1.9, 10.8)
Size: Small/Medium	0.5 (0.1, 1.5)
Size: Large/Medium	3.3 (1.6, 6.8)
Mechanism: Severe/(Mild/Moderate)	2.4 (1.2, 4.7)

APPLICABILITY: Results of this sub-analysis of the multicenter emergency department head trauma decision rule can likely be widely applied. The analysis was based on the “extensive” definition (See Appendix) of isolated scalp hematoma which differs from the definition used in the parent study. Use of the extensive definition limits the ability to directly compare risk of TBI on CT and ciTBI with the parent study.

AUTHOR’S CONCLUSIONS: “In conclusion, in this large prospective cohort of young children with blunt head trauma, we found that isolated scalp hematomas (ie, without other symptoms or signs of brain injury) are common, yet were very uncommonly associated with traumatic brain injuries requiring an acute medical intervention, particularly neurosurgery. There was, however, concern for non-accidental trauma in several children with traumatic brain injuries on CT. The data presented build on our previous study results and help to further identify children younger than 24 months who are at very low risk of clinically important traumatic brain injuries, for whom CT scan can be obviated or the decision to CT can be deferred until after a period of ED observation. The present study suggests that infants younger than 6 months with isolated scalp hematomas have a higher prevalence of clinically important traumatic brain injuries and traumatic brain injuries on CT than older infants. Those at particular risk include infants younger than 3 months with any scalp hematomas and older infants with larger temporal or parietal scalp hematomas. If a non-frontal scalp hematoma is present, specific factors such as older age, small hematoma size, and non-severe mechanism of injury should be used by clinicians to identify groups of children for whom CT typically appears unnecessary.”

POTENTIAL IMPACT: In children with an isolated scalp hematoma, age < 6 months, a non-frontal hematoma and a severe mechanism were independent predictors of TBI on CT. Clinically important traumatic brain injury was rare and all patients meeting criteria did so based on admission for more than 2 nights. None died, required a neurosurgical invention or intubation. The low rate of ciTBI precluded a regression analysis on this outcome which is the more clinically important outcome. The use of the extensive definition of isolated scalp hematoma instead of that used in the parent studies limits the ability to directly compare rates of TBI on CT and ciTBI. However, providers can be used to identified predictors in those with an isolated scalp hematoma to risk stratify those at high risk to aid in the decision on who to CT and who to observe. The PECARN rule and the high-risk predictors identified for patients with isolated scalp hematoma should be used with caution if at all in patients with suspected intentional trauma as the parameters of “acting normally as per parents” and the mechanism or injury may not be reliable.

APPENDIX: ISOLATED SCALP HEMATOMA DEFINITIONS

ISOLATED SCALP HEMATOMAS DEFINITIONS (< 24 MONTHS)	
EXTENSIVE DEFINITION	PECARN RULE-BASED DEFINITION
No signs or symptoms other than: Frontal, parietal, temporal, or occipital scalp hematoma	No signs or symptoms other than: Parietal, temporal, or occipital scalp hematoma defined by the PECARN prediction rule variables for children younger than 24 months
PATIENT MET ALL OF FOLLOWING	PATIENT MET ALL OF THE FOLLOWING
No history of any LOC	No LOC or LOC < 5 seconds
Acting normally per parent/guardian	Acting normally per parent/guardian
Pediatric GCS score of 15	Pediatric GCS score of 15
No signs of altered consciousness (e.g., sleepiness, agitation)	No signs of altered consciousness (e.g., sleepiness, agitation)
No palpable skull fracture	No palpable skull fracture
	No severe mechanism of injury
No signs of basilar fracture	
No neurologic deficits (e.g., motor or sensory abnormalities)	
No vomiting after the head trauma	
No seizure after the head trauma	

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

HEAD TRAUMA:
MACHINE LEARNING VS PECARN RULES

In patients < 18 years of age with acute, non trivial, blunt head trauma presenting to the Pediatric Emergency Department does a Machine Learning Derived Algorithm when compared to the PECARN Head TraumaDecision Rules accurately identify those with and without clinically important traumatic brain injury?

Michael Mojica, M.D.

August 2019

Bertsimas D, Dunn J, Steele DW, Trikalinos TA, Wang Y.

COMPARISON OF MACHINE LEARNING OPTIMAL CLASSIFICATION TREES WITH THE PEDIATRIC EMERGENCY CARE APPLIED RESEARCH NETWORK HEAD TRAUMA DECISION RULES.

JAMA Pediatr. 2019 Jul 1;173(7):648-656.
PubMed ID: 31081856

STUDY DEFINITIONS	
POPULATION	Inclusion: < 18 years of age Blunt head trauma within 24 hours of emergency department presentation GCS ≥ 14 Exclusion: Trivial mechanism (fall from ground level, walk, run into stationary object with no signs or symptoms other than scalp abrasions and lacerations) Penetrating trauma History of central nervous system tumor, preexisting neurologic disease Neuroimaging prior to presentation Setting: 25 Children's Hospital EDs in the PECARN network. PECARN: Derivation set: 6/2004-3/2006, Validation set: 3/2006-9/2006 Anonymized analysis of the PECARN Data Set: 9/2016-12/2018 (due to anonymization, this study did not use the original derivation and validation sets)
RULE PARAMETERS	Predictors: Age, sex, injury mechanism severity, seizure onset/duration, loss of consciousness, headache location/severity, skull fracture/hematoma size/location, altered mental status (GCS 14, agitation, somnolence, repetitive response to questioning, slow response to verbal commands). Excluded: Altered mental status category of "other" could not be operationalized Dizziness excluded due to insufficient interobserver agreement
REFERENCE STANDARD	1. CT at MD discretion. Interpreted by site faculty radiologists or study radiologist if inconclusive 2. If CT not obtained a. Discharged patients: Clinical follow up. Standardized telephone surveys at 7-90 days post ED visit. Evaluation of medical examiner records in unavailable b. Admitted patients: Hospital course Traumatic Brain Injury (TBI): Intracranial hemorrhage or contusion, cerebral edema, traumatic infarction, diffusive axonal injury, shearing injury, signs of brain herniation, diastasis of the skull, pneumocephalus or depressed skull fracture Clinically Important Traumatic Brain Injury (ciTBI): TBI above associated with: 1. Death 2. Neurosurgical intervention 3. Intubation for > 24 hours 4. Admission for > 48 hours
OUTCOME	Rule Characteristics: Separate rules for < 2 years of age, ≥ 2 years of age Comparison of Machine Learning and PECARN rule characteristics Potential decrease in head CT utilization
DESIGN	Observational: Retrospective cohort (analysis of prospectively collected data)

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes. An extensive list of predictors that would be available at presentation were included. The altered mental status category of “other” was excluded due to difficulty operationalizing this category. Dizziness was excluded due to insufficient interobserver agreement. 2 PECARN risk factors: “signs of basilar skull fracture” and “not acting normally as per parent” are not explicitly identified as potential predictors. However, both factors are included as decision nodes in the < 2 year old algorithm (Figure 1) and “signs of occipital skull fracture” is included in the < 2 year old algorithm (Figure 2). They are likely encompassed in “skull fracture” and “altered mental status”.
Were all important predictors present in significant proportion of the study population?	Unclear. (See Table 1 and 2 of the original PECARN Study, predictor prevalence by age category and study phase). Signs of basilar skull fracture seen in only 0.5% < 2 years and 0.7% ≥ 2 years. Only 3% of patients had a Glasgow Coma Scale of 14.
Were the outcome event and predictors clearly defined?	Yes. The outcomes of “traumatic brain injury” and “clinically important traumatic brain injury” were clearly defined.
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Yes. The study is retrospectively analyzing prospectively collected data. In the 2009 PECARN study, the case report form was completed prior to results of the CT if one was obtained. Follow-up on admitted and discharged patients was blinded to the presence of the predictors.
Was the sample size adequate (including an adequate number of outcome events)?	Unclear. In general, 10 outcomes per rule parameter is considered adequate in logistic regression. It is unclear if this rule applies to CART and ORT analysis. In the < 2 year age group 98 patients had ciTBI. 7 variable were included in the PECARN algorithm and 13 variables (including 4 different age cutoffs) were included in the ORT algorithm. In the ≥ 2 year age group 278 patients had ciTBI. 7 variable were included in the PECARN algorithm and 13 variables (including 4 different age cutoffs) were included in the ORT algorithm.

WHAT ARE THE RESULTS?

How well did the rule correctly identify patients <u>with</u> the primary outcome? How precise was this measurement?
How well did the rule correctly identify patients <u>without</u> the primary outcome? How precise was this measurement?

NOTE: PECARN Rule parameters are reported here as if a patient with ANY of the rule parameters is considered NOT VERY LOW RISK and a patient with NONE of the rule parameters is considered VERY LOW RISK. This would be considered a “directive” rule. The PECARN authors instead recommend the use of an “assistive” rule with 3 categories of risk in which providers have the option of observation or CT scan for the middle risk category.

<u>< 2 years</u>
N = 10,718 (Derivation: 8,502, Validation: 2,216)
ciTBI: 0.9% (98/10,017), 95% CI (0.8, 1.1%)

<u>≥ 2 years</u>
N = 31,694 (Derivation: 25,283, Validation: 6,411)
ciTBI: 0.9% (278/31,694), 95% CI (0.8, 1.0%)

The OCT group had statistically significant higher specificity, predictive value of a positive test and likelihood ratio of a positive test in both age cohorts. There was no statistically significant difference in OCT and PECARN in sensitivity, predictive value of a negative test and likelihood ratio of a negative test in either age cohorts. A rule was considered negative if it categorized a patients as “Very Low Risk” and positive if it categorized a patients as “Low Risk” or “Higher Risk”.

RULE CHARACTERISTICS (< 2 YEARS)			
DERIVATION SET	OCT	PECARN	RELATIVE EFFECT
Sensitivity	97.8% (92.8, 99.7%)	95.5% (90.8, 99.2%)	1.57 (0.34, 10.53)
Specificity	72.2% (71.2, 73.1%)	53.9% (52.8, 55.0%)	2.22 (2.13, 2.31)
Predictive Value (+) Test	2.9% (2.8, 3.1%)	1.8% (1.7, 1.8%)	1.68 (1.59, 1.78)
Predictive Value (-) Test	100% (99.9, 100%)	99.9% (99.9, 100%)	2.07 (0.48, 13.46)
Likelihood Ratio (+) Test	3.51 (3.31, 3.66)	2.09 (1.96, 2.17)	1.68 (1.59, 1.78)
Likelihood Ratio (-) Test	0.03 (0.0, 0.1)	0.06 (0.02, 0.17)	0.48 (0.07, 2.11)
VALIDATION SET	OCT	PECARN	RELATIVE EFFECT
Sensitivity	94.1% (81.7, 99.1%)	94.1% (81.7, 99.1%)	1.00 (0.16, 6.40)
Specificity	69.3% (67.4, 71.2%)	52.8% (50.8, 54.9%)	2.02 (1.87, 2.18)
Predictive Value (+) Test	3.4% (2.9, 3.7%)	2.2% (1.9, 2.4%)	1.54 (1.36, 1.74)
Predictive Value (-) Test	99.9% (99.7, 100%)	99.9% (99.6, 100%)	1.31 (0.23, 7.68)
Likelihood Ratio (+) Test	3.06 (2.63, 3.35)	1.99 (1.72, 2.14)	1.54 (1.36, 1.74
Likelihood Ratio (-) Test	0.09 (0.01, 0.26)	0.11 (0.02, 0.35)	0.76 (0.13, 4.44)
GREEN = Statistically Significant, RED = Not Statistically Significant			

RULE CHARACTERISTICS (≥ 2 YEARS)			
DERIVATION SET	OCT	PECARN	RELATIVE EFFECT
Sensitivity	95.6% (92.3, 97.8%)	96.0% (92.9, 98.1%)	0.90 (0.44, 1.75)
Specificity	65.5% (64.9, 66.1%)	57.8% (57.1, 58.4%)	1.39 (1.37, 1.42)
Predictive Value (+) Test	2.3% (2.2, 2.4%)	1.9% (1.8, 2.0%)	1.22 (1.18, 1.26)
Predictive Value (-) Test	99.9% (99.9, 100%)	99.9% (99.9, 100%)	1.02 (0.52, 1.94)
Likelihood Ratio (+) Test	2.77 (2.67, 2.85)	2.27 (2.19, 2.33)	1.22 (1.18, 1.26)
Likelihood Ratio (-) Test	0.07 (0.03, 0,12)	0.07 (0.03, 0.12)	0.98 (0.52, 1.93)
VALIDATION SET	OCT	PECARN	RELATIVE EFFECT
Sensitivity	94.5% (87.2, 98.3%)	94.5% (87.3, 98.3%)	1.00 (0.42, 2.40)
Specificity	65.6% (64.5, 66.8%)	57.6% (56.4, 58.8%)	1.41 (1.36, 1.46)
Predictive Value (+) Test	2.7% (2.4, 2.8%)	2.2% (2.0, 2.3%)	1.23 (1.17, 1.30)
Predictive Value (-) Test	99.9% (99.8, 100%)	99.9% (99.8, 100%)	1.14 (0.50, 2.62)
Likelihood Ratio (+) Test	2.75 (2.52, 2.90)	2.23 (2.05, 2.34)	1.23 (1.17, 1.30)
Likelihood Ratio (-) Test	0.08 (0.03, 0.19)	0.10 (0.03, 0.22)	0.88 (0.38, 2.01)
GREEN = Statistically Significant, RED = Not Statistically Significant			

RISK OF CITBI BY RISK CATEGORY*				
	< 2 YEARS		≥ 2 YEARS	
	OCT	PECARN	OCT	PECARN
Very Low Risk	0% (0/7,605)	0.017% (1/5,702)	0.048%(10/20604)	0.049% (9/18,143)
Low Risk	1.47% (31/2,100)	0.88% (31/3,524)	1.14% (80/6,994)	0.83% (76/9,106)
Higher Risk	6.61% (67/1,013)	4.42% (66/1,492)	4.58%(188/4096)	4.34% (193/4,445)
*Derivation and validation sets combined				

How would use of the rule impact resource utilization?

Proportion Categorized as Very Low Risk of ciTBI: < 2 years (Derivation + Validation Sets)
Absolute Risk ORT: 71% (7,605/10,718),CT rate = 29% (if Low risk and Higher risk CT'd)
Absolute Risk PECARN: 53.2% (5,702/10,718), CT rate 46.8% (if Low risk and Higher risk CT'd)
Absolute Risk Increase (AR ORT – AR PECARN) = 71% - 53.2%= 17.8%, 95% CI (16.5, 19%)
The authors report a Relative Risk Increase (RRI) of 33%.
RRI = ((AR ORT – AR PECARN)/(AR PECARN) = ((71% - 53.2%)/53.2%) = 33%)

Proportion Categorized as Very Low Risk of ciTBI: ? 2 years (Derivation + Validation Sets)
Absolute Risk ORT: 65% (20,604/31,694), CT rate 35% (if Low risk and Higher risk CT'd)
Absolute Risk PECARN: 57.2% (18,143/31,694), CT rate 42.8% (if Low risk and Higher risk CT'd)
Absolute Risk Increase (AR ORT – AR PECARN) = 65% - 57.2% = 7.8%, 95% CI (7.0, 8.5%)
The authors report a Relative Risk Increase (RRI) of 14%.
RRI = ((AR ORT – AR PECARN)/(AR PECARN) = ((65% - 57.2%)/57.2%) = 14%)

Was there an internal statistical validation of the results? How did it compare to the primary results?
Yes. Test characteristics of both the derivation and validation sets were very similar for each age category (See tables above). The large sample size generally resulted in narrow confidence intervals.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

At what level of development is this rule? How can it be applied? (See appendix)	☐ I ☐ II ☐ III ■ IV This is a level IV rule. “The rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods”. Level IV rules requires further validation before it can be applied clinically
Does the rule make clinical sense?	Yes. The rules do make clinical sense. Rule parameters are factors we typically consider defining risk for head trauma. However, the OCT algorithm included more parameters than the PECARN rules and would require incorporation into the electronic medical record or a separate calculator to utilized
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Some of the predictors are somewhat subjective. These include: scalp hematoma (none or barely palpable vs < 1 cm duration of loss of consciousness, acting normally as per parent, the altered mental status definition of sleepy or agitated and headache severity. Inter-rater reliability of the predictors in the final PECARN rules were moderate. The decision tree should include a legend defining altered mental status and severity of mechanism.
Is the rule applicable to the patients in my practice?	Yes. This study included ED patients at multiple sites throughout the U.S. Applicability to other clinical settings is unclear though the large sample size would appear to enhance generalizability of the rule.
Will the rule results change my management strategy?	The impact of the rule on management strategy will depend on the current approach to head trauma. The rules have the potential to standardize the approach to head trauma.
What are the benefits of applying the rule to my patients?	Similar to the PECARN rule the OCT algorithm would identify the majority of patients of patients with ciTBI. Compared to PECARN rule, the OCT rules had a higher proportion of patients classified as very low risk and could potentially lower the CT rate. The OCT rules require further validation and an impact analysis to determine the actual effect on CT utilization.
What are the risks of applying the rule to my patients?	Confidence intervals include the rare possibility of missing patients with ciTBI.

CLINICAL BOTTOM LINE

BACKGROUND: Pediatric mild, blunt head trauma is a common occurrence. Traumatic brain injury requiring an intervention is rare. Risks associated with unnecessary neuroimaging may be significant. The PECARN head trauma rules have been derived and externally validated and are used in a variety of settings (PECARN, Lancet. 2009, PubMed ID: 19758692). Machine learning techniques have the potential to derive rules of equivalent accuracy in identifying patients with clinical important traumatic brain injury and the potential to further decrease head CT utilization

CLINICAL QUESTION: In patients < 18 years of age with acute, non-trivial, blunt head trauma presenting to the Pediatric Emergency Department does a Machine Learning Derived Algorithm when compared to the PECARN Head Trauma Decision Rules accurately identify those with and without clinically important traumatic brain injury?

DESIGN/VALIDITY: This study was well designed using a machine learning approach. The authors describe optimal classification trees as analogous to classification and regression trees (CART analysis). The mixed integer classification tree (OCT) method has been proven to outperform CART fitting methods. OCT was tuned be as likely as PECARN to miss ciTBI with a true positive to false positive ratio of 500:1.

The study used the original PECARN data set but due to anonymization of the data, could not reproduce the original derivation and validation data sets. In addition, dizziness was exclude as a potential parameter due to poor interobserver reliability and the altered mental status category of “other” was excluded due to difficulty operationalizing this category.

The OCT risk cutoffs utilized were slightly different from those in the PECARN study (Very low risk: < 0.1%, Low risk: 0.1–3.0%, High risk: 3%). PECARN risk of ciTBI in patients < 2 year of age was 0.02% in the very low risk group (No CT), 0.8% in the low risk group (Observe or CT) and 4.3% in the high-risk group (Yes CT). PECARN risk of ciTBI in patients ≥ 2 year of age was 0.05% in the very low risk group (No CT), 0.9% in the low risk group (Observe or CT) and 4.4% in the high-risk group (Yes CT).

PRIMARY RESULTS: The less than 2 years of age cohort included 10,718 patients (Derivation: 8,502, Validation: 2,216) and had a rate of ciTBI of 0.9% (98/10,017), 95% CI (0.8, 1.1%). The greater than or equal to 2 years of age cohort included 31,694 patients (Derivation: 25,283, Validation: 6,411) and had a ciTBI rate of 0.9% (278/31,694), 95% CI (0.8, 1.0%)

In the < 2 year age cohort, 7 variables were included in the PECARN algorithm and 13 variables (including 4 different age cutoffs) were included in the ORT algorithm. In the ≥ 2 year age cohort 7 variables were included in the PECARN algorithm and 9 variables (including 2 different age cutoffs) were included in the ORT algorithm.

The OCT group had statistically significant higher specificity, predictive value of a positive test and likelihood ratio of a positive test in both age cohorts and in both the derivation and validation data sets. There was no statistically significant difference in OCT and PECARN in sensitivity, predictive value of a negative test and likelihood ratio of a negative test in either age cohorts. The PECARN rule parameters are reported as if a patient with ANY of the rule parameters is considered “Not Very Low Risk “and a patient with none of the rule parameters is considered “Very Low Risk”. This would be considered a “directive” rule.

The PECARN authors instead recommend the use of an “assistive” rule with 3 categories of risk in which providers have the option of observation or CT scan for the middle risk category.

The OCT algorithm was similar to PECARN in the rate of missed ciTBI. The OCT algorithm classified a greater proportion of patients as “very low risk” compared to PECARN. This has the potential to lead to a greater decrease in CT utilization using the OCT algorithm. In the less than 2 year ago cohort the increase in the proportion classified as “very low risk” by the OCT algorithm was 17.8%, 95% CI (16.5, 19%). In the greater than or equal to two years of age cohort the increase in the proportion classified as “very low risk” by the OCT algorithm was 7.8%, 95% CI (7.0, 8.5%)

APPLICABILITY: The PECARN rule appears sensible and easy to apply and included only 7 parameters in each age cohort. The ORT algorithm is more complex included a greater number of parameters and would require incorporation into the electronic medical record or a separate calculator to utilized. (WEBLINK: OCT RULE: CITBI RISK CALCULATOR). The subjectivity of some predictors may limit its usefulness and it is recommended that rules definitions for signs of altered mental status and mechanism of injury accompany the decision algorithm. Only 3.2% of patients had a GCS of 14 potentially limiting generalizability to this population.

The rules appear generalizable to a large variety of children though the applicability to no children’s hospital ED settings is unclear. This is a level IV rule. “The rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods”. Level IV rules requires further validation before it can be applied clinically

AUTHOR’S CONCLUSION “Optimal classification tree–based rules may have better predictive performance and provide personalized and more granular risk predictions than the PECARN rules. However, OCTs are inherently more complicated than the PECARN rules because they include more predictors (e.g., age), encode predictors in several levels instead of dichotomizing them, and examine interactions between predictors. In practice, OCTs would have to be integrated into the electronic health record to provide real-time personalized risk predictions. The OCTs are an alternative to the PECARN rules. Clinicians who are partial to using decision rules might value the simplicity of the PECARN rules and the accompanying treatment recommendations. Clinicians who are not willing to adopt the risk-benefit tradeoffs implied by the PECARN rules may prefer to obtain risk predictions and make decisions according to their own and the guardians’ preferences and risk attitudes. We surmise that large health systems that aim to optimize operations by capitalizing on better predictive performance would consider easy-to-use implementations of the OCTs in their systems.”

POTENTIAL IMPACT: When the PECARN head trauma rules were published I imagined them to be the definitive study of pediatric head trauma risk for the foreseeable future. They are easy to apply and have been derived and validated. The machine learning techniques used in this study were similar to the PECARN rule in not missing those with clinically important traumatic brain injury and classified a greater proportion of patients as “very low risk” compared to PECARN. This has the potential to lead to a greater decrease in CT utilization using the OCT algorithm. The ORT algorithm is more complex including a greater number of parameters and would require incorporation into the electronic medical record or a separate calculator to be utilized. Providers would need to overcome their mistrust of using a new classification technique this is not readily comprehensible.

APPENDIX: STAGE OF DEVELOPMENT AND APPLICABILITY OF CLINICAL DECISION RULES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

APPENDIX: RULE PARAMETERS

RULE PARAMETERS: PECARN	
< 2 YEAR	≥ 2 YEARS
GCS < 15	GCS < 15
Other signs of altered mental status	Other signs of altered mental status
Palpable skull fracture	Signs of basilar skull fracture
History of loss consciousness ≥ 5 seconds	History of loss consciousness
Severe mechanism of injury	Severe mechanism of injury
Not acting normally as per parent	History of vomiting
Non-frontal scalp hematoma	Severe headache

RULE PARAMETERS: MACHINE LEARNING OCT ALGORITHM	
< 2 YEAR	≥ 2 YEARS
Mechanism: Mild versus Moderate/Severe	Mechanism: Mild versus Moderate/Severe
Scalp hematoma: None/frontal vs OC/P/T*	Scalp hematoma: None/frontal/O vs P/T*
Signs of Basilar Skull Fracture: Yes vs No	Signs of Basilar Skull Fracture: Yes vs No
Altered Mental Status: Yes vs No	Altered Mental Status: Yes vs No
LOC: (None or 5 sec) vs > 5 sec*	LOC: (None or <5min) vs (> 5min or unknown)*
Age: < 1 month, ≥ 1 month	Age 26 months, > 26 months
Age: 6 months, > 6 months	Age 54 months, > 54 months
Age: 9 months, > 9 months	Headache: None/Mild vs Moderate/Severe
Age: 18 months, > 18 months	Vomiting: 0 vs ≥ 1
Sex: Male vs Female	
Palpable depressed skull fracture: Yes vs No	
Acting normal as per parents: Yes vs No	
Scalp hematoma (None/Barely Palpable v ≥1cm	
*Note: Difference parameter definitions	

HEAD TRAUMA:
POINT-OF-CARE US FOR SKULL FRACTURES

In children under two years of age with mild blunt head trauma (GCS 14-15) due to a non-trivial mechanism of injury and with focal signs of scalp trauma, can point-of-care ultrasound (POCUS) of the skull accurately identify skull fracture:

1. Presence (Yes/No)?
2. Type (linear, depressed or complex)?
3. Depth of depressed skull fractures?

Guillermo De Angulo MD, Rebecca Burton MD

August 2018

Parri N, Crosby BJ, Mills L, Soucy Z, Musolino AM, Da Dalt L, Cirilli A, Grisotto L, Kuppermann N.

POINT-OF-CARE ULTRASOUND FOR THE DIAGNOSIS OF SKULL FRACTURES IN CHILDREN YOUNGER THAN TWO YEARS OF AGE.

J Pediatr. 2018 May;196:230-236.e2.
PubMed ID: 29499992

STUDY DEFINITIONS	
POPULATION	Inclusion: Age < 2 years GCS score of 14-15 after minor blunt head trauma Non-trivial mechanism of injury Localizing evidence of scalp trauma: cephalohematoma, focal pain, deformity Undergoing cranial CT scan as determined by the attending physician (encouraged use of PECARN head trauma rule to standardize decision making) Exclusion: Trivial mechanism: Ground level falls or walking/running into stationary objects and no signs of traumatic brain injury Open skull deformity or fracture, penetrating trauma Known brain tumors Pre-existing neurological disorders complicating assessment Ventricular shunts Bleeding disorders Setting: Multicenter study (6): Italy (3), US (3), 1 general and 5 pediatric EDs 5/2013-4/2015
DIAGNOSTIC TEST	Point of Care Ultrasound Who: General or pediatric ED faculty or residents When: Prior to CT (if possible) Training: Varying degrees of prior ultrasound experience 2 of 20 with skull fracture ultrasound experience 2 video didactic training sessions Hands on training sessions at each site Demonstration of 10 successful skull ultrasounds as judged by the site lead Equipment: High frequency linear transducer Technique: Over focal area of concern based on clinical findings Extended to immediate surrounding area if fracture not identified Contralateral skull used to distinguish fractures from sutures Interpretation: Fracture presence (Yes/No): Cortical irregularity in multiple orientations Fracture type: Linear, depressed, complex Fracture depth: 3 mm, 4-6 mm, 7-10 mm, ≥ 11 mm
REFERENCE STANDARD	Non-contrast head CT Scan
OUTCOME	Test characteristics for fracture presence/absence Accuracy for fracture type and depth
DESIGN	Observational: Prospective Cohort

HOW SERIOUS WAS THE RISK OF BIAS?	
Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Unclear. The presence of a palpable fracture (step-off or depression) would be an indication for a CT by the PECARN head trauma rule for those less than 2 years of age. In this situation there would not be a diagnostic dilemma and an ultrasound may not influence the decision to obtain a head CT. In this study, 21/115 (18.3%) had a palpable skull fracture. 71.4% of those with a palpable fracture were depressed fractures. These patients would need a CT regardless of the ultrasound result.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. The study compared POCUS to a non-contrast head CT scan. This is the independent reference standard that is used to diagnose both skull fractures and traumatic brain injury. There was no measure of inter-rater reliability of head CT interpretation.
Were those interpreting the test and reference standard blind to the other results?	Yes. Ideally the POCUS was completed prior to the CT scan. When the CT scan was done prior to the POCUS or the treating physician already knew the results (e.g. CT scan obtained prior to transfer in), another sonographer that was blinded to the CT scan results performed the study. However, the fact that a patient had been transferred (14/215) from an outside hospital may imply that the patient had an injury identified on CT scan and could potentially bias ultrasound interpretation.
Did all patients regardless patients receive the same reference standard irrespective of the test results?	Yes. The study inclusion criteria required that a head CT was ordered based on clinical assessment. There would be no reference standard without the head CT. Since majority of the skull fractures did not required intervention, clinical follow up would not have been sufficient as an alternative reference standard. Additionally, it would not be ethical to irradiate a patient when the a head CT was not clinically indicated.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

N = 115 patients (Italy: 87, US: 28), N = 20 ultrasonographers
Mean age: 7.9 ± 6.2 months, 54% male
Mechanism: Fall from elevation (74.8%), fall down stairs (9.6%)
Neurosurgical intervention (8.7%): Fracture elevation (7.8%), epidural evacuation (0.9%)
Fracture Characteristics:
1. Prevalence: 88/115 (76.5%), 13.6% of which with > 1 fracture
2. Type: Linear (64.3%), depressed (29.8%)(89.3% 3 mm) , complex (14.3%)
3. Location: Frontal (4.6%), Temporal (3.4%), Parietal (75.9%), Occipital (16.1%)
Exam Characteristics:
Scalp hematoma or swelling: 106/115 (93.8%), < 1cm (7%), 1-3 cm (50%), > 3 cm (43%)
Palpable skull fracture: 21/115 (18.3%) had a palpable skull fracture (71.4% of which depressed)
CT Characteristics:
1. CT with Skull fracture: 76.5% (88/115) of patients with 127 abnormal findings
   a. Fracture alone: 63.6% (56/88)
   b. Fracture with addition findings: 36.3% (32/88), Fx + 1 (30.7%), Fx + 2 (4.5%), Fx + 4 (1.1%)

		Head CT		
		Fracture YES	Fracture NO	
Point of Care Ultrasound	Fracture YES	80	4	84
	Fracture No	8	23	31
		88	27	115

TEST CHARACTERISTIC	CALCULATION	POINT ESTIMATE (95% CI)
Prevalence	88/115	76.5% (68.0, 83.3%)
Sensitivity	80/88	90.9% (82.9, 96%)
Specificity	23/27	85.2% (66.3, 95.8%)
Predictive Value (+) Test	80/84	95.2% (88.3, 98.7%)
Predictive Value (-) Test	23/31	74.2% (55.4, 88.1%)
Likelihood Ratio (+) Test	(80/88)/(4/27)	6.14 (2.48, 15.2)
Negative Likelihood (-) Test	(8/88)/(23/27)	0.11 (0.05, 0.21)

The point of care ultrasound essentially took a population with a 76.5% prevalence of skull fractures and stratified it into a high risk population if the POCUS was positive (PV (+) = 95.2%) and a low risk population if the POCUS was negative (1-PV(-) = 100 – 74.2 = 25.8%). One quarter of the patients with a negative POCUS had a skull fracture.

The 8 fractures that POCUS did not identify were isolated linear skull fractures that were not in the scanned area and did not require further intervention. Whether these fractures were associated with intracranial injury was not provided. The clinical significance of these fractures is unclear.

Agreement: Fracture Type: Kappa 0.75, 95% CI (0.70.0.84)
Agreement: Fracture depth: 3 mm (kappa 0.69, 95% CI (0.52, 0.85))
4-6 mm (kappa 1.0, confidence interval could not be calculated)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Unclear. The investigators did not present a kappa as a measure of inter-rater reliability for ultrasound interpretation. They also did not provide a breakdown of who performed most of the ultrasounds (novice versus expert, general pediatrician vs ED physician vs resident). There was also no description of fracture size so the spectrum bias cannot be excluded.
Are the study results applicable to the patients in my practice?	Unclear. Since no objective criteria was used to determine who required a CT scan, we do not truly know what type of patients were enrolled. Clinicians were encouraged, but not required, to use the PECARN head trauma rule to guide CT utilization. This was a high risk population with a skull fracture rate of 76.5%. 8.7% of patients required neurosurgical intervention. Since, Europeans have utilized ultrasound more extensively and for a longer period of time, the predominance of Italian sonographers may limit the of generalize to providers in the US.
Will the test results change my management strategy?	No. It is difficult to determine a situation in which skull POCUS would change my management strategy given the study's limitations. One quarter of patients with a negative POCUS had a skull fracture. A patient with a large hematoma, bone step off or depression and a negative POCUS will likely still require a head CT. A point of care ultrasound that is positive will definitely require a head CT because of the high risk of associated intracranial injury.
Will patients be better off as a result of the test?	A bedside, diagnostic test that reduces CT scan rates and radiation exposure would be attractive. However, as discussed above the study has multiple limitations. This includes many generalizability issues and a high rate of missed fractures in those with a negative POCUS.

CLINICAL BOTTOM LINE

BACKGROUND: Blunt head trauma is a common pediatric presentation to emergency departments with a quarter of patients younger than 2 years of age. The risk of skull fracture is inversely proportional to age and skull fractures are a risk factor for intracranial injury. A follow-up study to the pediatric head trauma decision rule identified risk factors for intracranial injury in patients with isolated scalp hematomas. Significant predictors included: age < 6 months, non-frontal location, size greater than 3 cm and severe mechanism of injury (Ann Emerg Med. 2014, PubMed ID: 24635991). The current reference standard for diagnosing both skull fractures and traumatic brain injury (TBI) in children is a non-contrast head CT. However, ionizing radiation is associated with an increases the lifetime risk of CNS malignancy with younger patients are at highest risk. Studies of point of care ultrasound for evaluation of skull fractures in children have shown promising results that if validated may help risk stratify children for TBI following blunt head trauma (Rabiner, Pediatrics 2013, PubMed ID: 23690519).

CLINICAL QUESTION: In children under two years of age with mild blunt head trauma (GCS 14-15) due to a non-trivial mechanism of injury and with focal signs of scalp trauma, can point-of-care ultrasound (POCUS) of the skull accurately identify skull fracture:
1. Presence (Yes/No)?
2. Type (linear, depressed or complex)?
3. Depth of depressed skull fractures?

DESIGN/RISK OF BIAS: This was a multicenter, prospective cohort study conducted in both Italy and the US. The study included children less than 2 years of age with a GCS score of 14-15 after minor blunt head trauma with a non-trivial mechanism of injury and evidence of scalp trauma including cephalohematoma, focal pain or deformity. All patients had a CT scan as determined by the attending physician. Clinicians were encouraged, though not mandated, to use the PECARN head trauma rule to standardize decision making. Point of care ultrasound was performed by residents and faculty with varying levels of prior ultrasound experience. 10% (2/20) had prior experience with point of care skull ultrasound. Training included 2 videos, hands on training sessions and demonstration of 10 successful skull ultrasounds. The primary outcome was the test characteristics for fracture presence. Secondary outcomes included agreement on fracture type and death.

In this study, 21/115 (18.3%) had a palpable skull fracture. 71.4% of those with a palpable fracture were depressed fractures. These patients would need a CT regardless of the ultrasound result so there was not a diagnostic dilemma.

PRIMARY RESULTS: 76.5% (88/115) of patients had skull fractures. The most common mechanism of injury was fall from elevation (74.8%). Scalp hematoma or swelling was present in 93.8% (106/115) and palpable skull fractures in 18.3% (21/115) (18.3%), 71.4% of which were depressed. Parietal fractures were the most common location (75.9%). Linear skull fractures were the common (64.3%) followed by depressed skull fractures (29.8%)(89.3% 3 mm) and complex skull fractures (14.3%). 88 patients with skull fractures had 127 abnormal CT findings. 63.6% with s skull fracture alone and 36.3% with a skull fracture and additional CT findings. 8.7% required neurosurgical intervention (fracture elevation (7.8%), epidural hematoma evacuation (0.9%)). The test characteristics for skull POCUS are provided in the table below.

TEST CHARACTERISTIC	CALCULATION	POINT ESTIMATE (95% CI)
Prevalence	88/115	76.5% (68.0, 83.3%)
Sensitivity	80/88	90.9% (82.9, 96%)
Specificity	23/27	85.2% (66.3, 95.8%)
Predictive Value (+) Test	80/84	95.2% (88.3, 98.7%)
Predictive Value (-) Test	23/31	74.2% (55.4, 88.1%)
Likelihood Ratio (+) Test	(80/88)/(4/27)	6.14 (2.48, 15.2)
Negative Likelihood (-) Test	(8/88)/(23/27)	0.11 (0.05, 0.21)

The point of care ultrasound essentially took a population with a 76.5% prevalence of skull fractures and stratified it into a high risk population if the POCUS was positive (PV (+) = 95.2%) and a low risk population if the POCUS was negative (1-PV(-) = 100 – 74.2 = 25.8%). One quarter of the patients with a negative POCUS had a skull fracture.

The 8 fractures that POCUS did not identify were isolated, linear skull fractures that were not in the scanned area and did not require further intervention. Whether these fractures were associated with intracranial injury was not provided and it is unclear if missing these fractures is acceptable.

Agreement between POCUS and CT to identify the type of fracture as linear, depressed or complex had a kappa of 0.75 (95% CI 0.70-0.84). Agreement between POCUS and CT to identify fracture depth had a kappa of 0.69, 95% CI (0.52, 0.85)) for fractures depressed 3 mm and a kappa of 1.0 (the confidence interval could not be calculated) for fractures depressed 4-6 mm.

APPLICABILITY: The primary concern with this study is it's generalizability. This was a select population with a high rate of skull fractures (76.5%) and neurosurgical intervention (7.8%). Indications for head CT were not presented. It would have been helpful to know the proportion of patient with an isolated scalp hematoma and no other risk factors. Use of the PECARN head trauma rule guide deciding whether to obtain a head CT was recommended, though not mandated.

The authors also did not specify who performed the head ultrasounds. 90% of the sonographers were novices for skull ultrasound prior to the study. Inter-rater reliability for POCUS was not presented. The majority (75.6%) of patients were enrolled in Italy. Europeans have utilized ultrasound more extensively and for a longer period of time. The predominance of Italian sonographers may limit the of generalize to providers in the US. In addition, fracture size was not presented introducing the possibility of spectrum bias.

AUTHOR'S CONCLUSION: "In summary, POCUS of the skull performed by physicians with dedicated training identifies skull fractures in infants with external signs of head trauma with substantial accuracy. Skull POCUS is able to detect the type and depth of fractures as identified on CT scan. POCUS allows rapid bedside assessment of the fracture and, in conjunction with head trauma clinical prediction rules, has implications for the escalation of care or further imaging if positive, and the possibility of obviating CT scanning if negative. The information provided by POCUS is easy to obtain and clinically meaningful, even if only to counsel parents that the child has a skull fracture and potentially establish closer follow-up. Clinicians working in ED settings should consider skull POCUS as an adjunct to clinical evaluation and clinical prediction rules for TBI to correctly risk stratify patients, identify those at risk of TBIs early, and reduce unnecessary exposure to radiation for those not at significant risk."

POTENTIAL IMPACT: The potential to reduce CT utilization with the use of point-of-care skull ultrasound is attractive. This population has the highest risk of radiation associated malignancy. However, at this time it unclear the point of care skull ultrasound would influence clinical decision making. A quarter of patients with a negative POCUS had a skull fracture. The missed fractures were isolated, linear skull fractures that were not in the scanned area and did not require further intervention. Whether these fractures were associated with intracranial injury was not provided and it is unclear if missing these fractures is acceptable

A point of care ultrasound that is negative in a patient with a large hematoma, bone step off or depression will likely still require a head CT. A point of care ultrasound that is positive will definitely require a head CT because of the high risk of associated intracranial injury.

HEAD TRAUMA:
DELAYED TBI PREDICTORS

In children less than 18 years old presenting to the ED more than 24 hours after head injury, do history and physical exam factors predict those with traumatic brain injury on CT scan (TBI CT) and clinically important TBI (ciTBI) when compared to patients presenting within 24 hours of head injury?

Mariju Baluyot, MD, Michael Mojica, M.D
October 2019

Borland ML, Dalziel SR, Phillips N, Lyttle MD, Bressan S, Oakley E, Hearps SJC, Kochar A, Furyk J, Cheek JA, Neutze J, Gilhotra Y, Dalton S, Babl FE; Paediatric Research in Emergency Department International Collaborative (PREDICT) Group

DELAYED PRESENTATIONS TO EMERGENCY DEPARTMENTS OF CHILDREN WITH HEAD INJURY: A PREDICT STUDY.

Ann Emerg Med. 2019 Jul;74(1):1-10.
PubMed ID: 30655017

STUDY DEFINITIONS	
POPULATION	Inclusion: Children < 18 years with head injury of any severity Exclusion: GCS <14, re-presentations to the ED for the same injury (could have presented < 24 hours to a non-ED setting) Setting: 10 pediatric Eds (Australia, New Zealand) in the PREDICT research network (Paediatric Research in Emergency Department International CollaboraTive, 4/2011-11/2014.
RULE PARAMETERS	Rule parameters from the PECARN, CATCH and CHALICE pediatric head trauma decision rules were included. These included: Age, sex, vomiting, LOC, headache, amnesia, seizure, nonaccidental injury concern, altered mental state (such as drowsiness or abnormal GCS score), exam suggestive of depressed skull fracture, abnormal neuro exam, presence of nonfrontal scalp hematoma. It is unclear if the parameter “acting normally as per parents” was assessed and suspected nonaccidental trauma was not included in PECARN
REFERENCE STANDARD	1. CT at MD discretion 2. Clinical follow-up of discharged patients. 3. Hospital course for admitted patients Traumatic Brain Injury on CT (TBI CT)* Intracranial hemorrhage or contusion, cerebral edema, traumatic infarction, diffuse axonal injury, shearing injury, sigmoid sinus thrombosis, signs of brain herniation, midline shift, diastasis of the skull, pneumocephalus, and depressed skull fracture. Clinically Important Traumatic Brain Injury (ciTBI)* 1. Death 2. Intubation for TBI >24 hours 3. TBI-related hospital admission for ≥ 2 nights 4. Neurosurgery: ICP monitoring, craniotomy, hematoma evacuation, elevation of depressed skull fracture, dura repair, tissue debridement, and lobectomy) *Definitions of TBI CT and ciTBI are identicle to PECARN head trauma rule with the exception of the fall height required to be a high risk injury mechanism PREDICT: < 1 meter, 1-1.5 meters, 1.5-3 meters, > 3 meters PECARN: > 0.9 meters (< 2 years), > 1.5 meters (> 2 years)
OUTCOME	1. Comparison: Prevalance of TBI CT and ciTBI (< 24 hrs vs > 24 hrs) 2. Predictors of TBI CT and ciTBI > 24 hrs 3. Test characteristics of statistically significant predictors
DESIGN	Observational: Prospective cohort (a secondary analysis of the Australasian Paediatric Head Injury Rule Study cohort)

HOW SERIOUS WAS THE RISK OF BIAS?	
Were all important predictors included in the derivation process?	Yes (Table 1). Predictors identified by the PECARN, CATCH and CHALICE head trauma rule were included: age, sex, vomiting, mechanism of injury, loss of consciousness, any amnesia, altered mental status, non-frontal scalp hematoma, exam suggestive of a depressed skull fracture and abnormal neurologic exam. The parameter “not acting normally as per parent” in the < 2 year old PECARN cohort was not included. The parameter of suspected non-accidental trauma was not included in PECARN
Were all important predictors present in significant proportion of the study population?	No. Logistical regression analyses were undertaken but could not be completed because predictors and outcomes had rare frequency (cell sizes were violated). Suspected non-accidental trauma 0.4% (<24hr) and 1.4% (>24 hr), altered mental status: 2.7 % (<24 hr) and 2.3% (>24 hr) were infrequent making it difficult to draw conclusions about these predictors
Were the outcome event and predictors clearly defined?	Yes. Outcomes were clinically important traumatic brain injury and CT evidence of brain injury with definition listed above as defined by the PECARN study with the exception of height of fall required to be a high risk mechanism of injury
Were those assessing the outcome event blinded to the presence of the predictors and were those assessing the presence of predictors blinded to the outcome event?	Yes. ED physicians were blinded to outcome event as they completed a case report form to collect predictive clinical data prior to imaging. Research assistants were presumably not blinded as they recorded ED and hospital management data after the visit and conducted telephone follow-up for patients who did not undergo imaging. No blinding to the predictors by outcome assessors would likely not affect the interpretation of TBI CT and ciTBI.
Was the sample size adequate (including an adequate number of outcome events)?	No. Using the criteria for logistic regression, an adequate sample size is generally considered to be 10 outcomes for every predictor. The l ow sample size precluded the use of logistic regression. TBI CT: 1 significant predictor, 37 with TBI CT ciTBI: 2 significant predictors, 8 with ciTBI

WHAT ARE THE RESULTS?

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SENSITIVITY AND PREDICTIVE VALUE OF A NEGATIVE RULE WITH 95% CONFIDENCE INTERVALS)
HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SPECIFICITY AND PREDICTIVE VALUE OF A POSITIVE RULE WITH 95% CONFIDENCE INTERVALS)

N=918 (> 24 hours), Female: 39.6%, < 2 years: 28.3%
CT Rate:
> 24 hours: 21.7%, 95% CI (19.1, 24.3%)
< 24 hours: 8.6%, 95% CI (8.2, 9.0%)

SIGNIFICANT DIFFERENCES BETWEEN EARLY AND LATE PRESENTERS (TABLE 1)

Parameter	> 24 hours	< 24 hours	Risk Difference (95%CI)
Non-frontal scalp hematoma	20.8%	18.1%	2.7 % (0.1, 5.3%)
Headache	31.6%	19.9%	11.7% (8.8, 14.7%)
Any vomiting	30.0%	16.3%	13.7% (10.8, 16.6%)
Non-accidental injury concern	1.4%	0.4%	1.0% (0.3, 1.7%)
Loss of consciousness*	11.4%	13.5%	-2.1% (-4.2, 0.0%)
Amnesia	6.3%	8.2%	-1.9% (-3.5, -0.3%)

GREEN = Statistically Significant, RED = Not Statistically Significant
*Discrepancy: Text indicates 13.5% vs 14.3%

COMPARISON: OUTCOME PREVALENCE (TABLE 2)

	TBI CT	ciTBI
> 24 hours	3.8% (37/981), (2.6, 5.0%)[1]	0.8% (8/981) (0.3, 1.4%)[2]
< 24 hours	1.2% (233/18,784), (1.1, 1.4%)	0.8% (151/18,784) (0.7, 0.9%)
Risk Difference (95%CI)	2.53% (1.33, 3.73%)	0.1%, (-0.57, 2.02%)
Odds Ratio (95%CI)	3.1 (2.2, 4.4)	1.0,(0.5, 2.0)

GREEN = Statistically Significant, RED = Not Statistically Significant
1. Most common: Intracranial hemorrhage/contusion (31), depressed skull fracture (8),
2. Hospital stay > 48 hrs for TBI (8), Neurosurgery (2), Intubation > 24 hrs for TBI (0), Death (0)

SIGNIFICANT PREDICTORS: PRESENTING AFTER 24 HOURS OF INJURY (TABLE 5)			
	TBI CT	ciTBI	ciTBI
Predictor	Non-frontal Scalp Hematoma	Non-frontal Scalp Hematoma	Concern Depressed Skull Fracture
Prevalence	3.8% (2.6, 5.0%)	0.8% (0.3, 1.4%)	0.8% (0.3, 1.4%)
Sensitivity	81.1% (65.8, 90.5%)	75.0% (40.9, 92.9%)	12.5% (2.2, 47.1%)
Specificity	81.6% (79.0, 89.3%)	79.7% (77.0, 82.1%)	99.3% (98.5, 99.7%)
Predictive Value (+)	14.7% (10.5, 20.2%)	2.9% (1.4, 6.3%)	12.5% (2.2, 47.1%)
Predictive Value (-)	99.1% (98.2, 99.6%)	99.7% (99.1, 99.9%)	99.3% (98.5, 99.7%)
Likelihood Ratio (+)	4.41 (3.58, 5.40)	3.69 (2.42, 5.60)	17.9 (2.5, 125.39)
Likelihood Ratio (-)	0.23 (0.12, 0.45)	0.31 (0.09, 1.04)	0.88 (0.68, 1.15)
Odds Ratio	19.0 (8.2, 43.9)	11.7 (2.4, 58.6)	19.7 (2.1, 182.1)
GREEN = Statistically Significant, RED = Not Statistically Significant Test characteristics calculated from Table 5 data: CEBM DIAGNOSTIC TEST CALCULATOR			

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?
The authors did not create a rule from their predictor values. The absence of the predictors for TBI CT and ciTBI had high predictive values of a negative test indication and low post test probability of the outcomes. However, the lower limits of the confidence intervals allow for a small percentage of patients to be missed.
WAS THERE AN INTERNAL STATISTICAL VALIDATION OF THE RESULTS? HOW DID IT COMPARE TO THE PRIMARY RESULTS?
There was not an internal statistical validation of the results.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (See Appendix)	▫ I ▫ II ▫ III ▫ IV Not applicable. The authors identified predictor variables but did not create a decision rule.
Does the rule make clinical sense?	The identified predictor variables make clinical sense. A concern for a depressed skull fracture has been associated with TBI CT and ciTBI. A non-frontal scalp hematoma is associated with TBI CT and ciTBI in the less than 2 year old PECARN cohort but not the greater than 2 years old. Of the 8 patients with ciTBI (Table 4) 1 of the 5 patients over two years of age had an isolated non-frontal scalp hematoma.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	Reproducibility of non-frontal scalp hematoma and suspected depressed skull fracture was not assessed. However, PECARN predictors were only included if they had a kappa of greater than 0.6.
Is the rule applicable to the patients in my practice?	The neuroimaging rate is lower in Australian/New Zealand studies than in US. In the PECARN study, 35% of children presenting < 24 hours with head trauma were scanned compared to 8.5% of children presenting <24 hours with head trauma and 21.7% of children presenting >24 hours in this study. The lower CT rate in the PREDICT cohort likely resulted in a lower rate of TBI CT (1.2%, 95% CI (1.1, 1.4%)) compared to PECARN (5.2%, 95% CI (4.9, 5.6%) in those presenting within 24 hours of injury. This also likely explains the higher rate of TBI CT in those presenting after 24 hours of injury (3.8%) 95% CI. (2.6, 5.0%). Interestingly, the overall PRECICT TBI CT rate of 5% (1.2% < 24hours + 3.8% after 24 hours) is similar to the PECARN TBI CT rate (5.2%). The PREDICT ciTBI rate in those presenting within 24 hours of injury of 0.8% (0.3, 1.4%) and those presenting after 24 hours of injury of 0.8%, 95% CI (0.7, 0.9%) is comparable to the PECARN ciTBI rate of 0.9%, 95% CI (0.8, 1.0%).
Will the rule results change my management strategy?	A patient with a suspected depressed skull fracture would have gotten a CT regardless of the study results. The PECARN rule did not indentify a non-frontal hematoma as a predictor of ciTBI in the older than 2 year cohort.
What are the benefits of applying the rule to my patients?	The absence of the identified predictors suggests a lower risk of ciTBI. The post test probability of ciTBI was 0.3% 95% CI (0.1, 0,3%) for non-frontal scalp hematoma and 0.7%% (0.3, 1.5%) for suspected depressed skull fracture. There is a potential to forego CT and radiation exposure in patients without these risk factors. Since a regression analysis was not performed it is difficult to assess the the interaction of these factors with other predictors.
What are the risks of applying the rule to my patients?	The probability of ciTBI in the absence of the identified predictors is not zero. What is an acceptable miss rate is debatable.

CLINICAL BOTTOM LINE

BACKGROUND: Blunt head trauma in the pediatric patient is a common presentation to emergency department. Clinical decision rules such as the PECARN rule (Lancet. 2009, PubMed ID: 19758692), CATCH rule (CMAJ 2010, PubMed ID: 20142371) and CHALICE rule (Arch Dis Child 2006, PubMed ID: 17056862) identified predictor variables for traumatic brain injury on CT (TBI CT) and clinically important traumatic brain injury (ciTBI). These rules have been validated and are used to guide the decision for CT scanning in the pediatric patient, weighing the risks and benefits of radiation exposure in this sensitive population. However The PECARN and CATCH decision rules and were derived in patients presenting within 24 hours of injury. The CHALICE rule (did not exclude patient presenting after 24 hours from injury but did not analyze them separately. This study aims to determine the prevalence of TBI and clinically important TBI in pediatric patients with delayed ED presentations compared to early representation for head trauma and determine which predictor variables from previously published clinical decision rules may identify those at increased risk of TBI CT and ciTBI inorder to guide imaging decisions.

CLINICAL QUESTION: In children less than 18 years old presenting to the ED more than 24 hours after head injury, do history and physical exam factors predict those with traumatic brain injury on CT scan and clinically important TBI when compared to patients presenting within 24 hours of head injury?

DESIGN/RISK OF BIAS: This was a prospective, observational cohort study, a secondary analysis of the Australasian Paediatric Head Injury Rule Study cohort. Predictor variables that were analyzed included those from the PECARN, CATCH and CHALICE pediatric head trauma decision rules. There included: age, sex, vomiting, loss of consciousness, headache, amnesia, seizure, nonaccidental injury concern, altered mental state (such as drowsiness or abnormal GCS score), exam suggestive of depressed skull fracture, abnormal neurologic exam, and presence of nonfrontal scalp hematoma. The reference standard was CT (at the clinicians discretion), hospital course for admitted patients and phone follow-up for discharged patients. TBI CT and ciTBI were as defined previously in the PECARN head trauma study.

PRIMARY RESULTS: 981 pediatric patients presented 24 hours after head injury. 37 patients (3.8%, 95% CI 2.6-5.0%) had TBI CT and 8 (0.8%, 95% CI 0.4-1.6%) had clinically important TBI with 2 patients (0.2%, 95% CI 0.0-0.5%) requiring neurosurgical intervention. Those presenting within 24 hours were statistically less likely to have TBI CT (1.2%, 95% CI(1.1, 1.4%) but there was no difference in the rate of ciTBI 0.8%, 95% CI (0.7, 0.9%)). The small number of patients with TBI CT and ciTBI precluded the use of regression anaylysis and did not allow for the cohort to be divided into less than two years and greater than 2 years as are the PECARN decision rules.

Patients presenting after 24 hours were statistically more likely to have a non-frontal scap hematoma, vomiting, headache and a suspicion of nonaccidental trauma when compared to those presenting within 24 hours of injury. Patients presenting after 24 hours were statistically less likely to have a loss of consciousness and amnesia when compared to those presenting within 24 hours of injury.

In the bivariable analysis, TBI CT was statistically more likely in those with a non-frontal scalp hematoma presenting after 24 hours (Odds Ratio 19.0, 95% CI (8.2, 43.9). ciTBI was statistically more likely in those with a non-frontal scalp hematoma (Odds Ratio: 11.7, 95% CI (2.4, 58.6) and in those with a suspected depressed skull fracture (Odds Ratio: 19.7, 95% CI(2.1, 182.1) presenting after 24 hours.

There was no statistically significant association in any other of the predictors analyzed. The lower limits of the 95% confidence intervals for the negative predictive values allows for a small percentage of those with TBI CT and ciTBI to be missed. Whether this miss rate is acceptable is a matter of judgement.

The impact of these predictors on neuroimaging decisions is unclear. It is likely that anyone with a suspected depressed skull fracture would have a head CT scan regardless of this study's results. In addition, a non-frontal scalp hematoma was a predictor of ciTBI in the PECARN cohort less than 2 years but not the cohort greater than twp years. One of the five patients with ciTBI over 2 years of age had an isolated non-frontal scalp hematoma.

SIGNIFICANT PREDICTORS: PRESENTING AFTER 24 HOURS OF INJURY (TABLE 5)

	TBI CT	ciTBI	ciTBI
Predictor	Non-frontal Scalp Hematoma	Non-frontal Scalp Hematoma	Concern Depressed Skull Fracture
Prevalence	3.8% (2.6, 5.0%)	0.8% (0.3, 1.4%)	0.8% (0.3, 1.4%)
Sensitivity	81.1% (65.8, 90.5%)	75.0% (40.9, 92.9%)	12.5% (2.2, 47.1%)
Specificity	81.6% (79.0, 89.3%)	79.7% (77.0, 82.1%)	99.3% (98.5, 99.7%)
Predictive Value (+)	14.7% (10.5, 20.2%)	2.9% (1.4, 6.3%)	12.5% (2.2, 47.1%)
Predictive Value (-)	99.1% (98.2, 99.6%)	99.7% (99.1, 99.9%)	99.3% (98.5, 99.7%)
Likelihood Ratio (+)	4.41 (3.58, 5.40)	3.69 (2.42, 5.60)	17.9 (2.5, 125.39)
Likelihood Ratio (-)	0.23 (0.12, 0.45)	0.31 (0.09, 1.04)	0.88 (0.68, 1.15)
Odds Ratio	19.0 (8.2, 43.9)	11.7 (2.4, 58.6)	19.7 (2.1, 182.1)

GREEN = Statistically Significant, RED = Not Statistically Significant
Test characteristics calculated from Table 5 data: CEBM DIAGNOSTIC TEST CALCULATOR

APPLICABILITY: It may be difficult to apply these results to our practice because the neuroimaging rate is lower in Australian/New Zealand studies than in United States. In the PECARN study, 35% of children presenting less than 24 hours with head trauma were scanned compared to 8.5% of children presenting within 24 hours with head trauma and 21.7% of children presenting after 24 hours in this study.

The lower CT rate in the PREDICT cohort likely resulted in a lower rate of TBI CT (1.2%, 95% CI (1.1, 1.4%)) compared to PECARN (5.2%, 95% CI (4.9, 5.6%) in those presenting within 24 hours of injury. This also likely explains the higher rate of TBI CT in those presenting after 24 hours of injury (3.8%) 95% CI. (2.6, 5.0%). Interestingly, the overall PRECICT TBI CT rate of 5% (1.2% < 24hours + 3.8% after 24 hours) is similar to the PECARN TBI CT rate (5.2%).

The PREDICT ciTBI rate in those presenting within 24 hours of injury of 0.8% (0.3, 1.4%) and those presenting after 24 hours of injury of 0.8%, 95% CI (0.7, 0.9%) is comparable to the PECARN ciTBI rate of 0.9%, 95% CI (0.8, 1.0%).

Reproducibility of non-frontal scalp hematoma and suspected depressed skull fracture was not assessed. However, PECARN predictors were only included if they had a kappa of greater than 0.6.

AUTHOR'S CONCLUSION: "Delayed presentation greater than 24 hours after head injury in children, although infrequent, may be significantly associated with traumatic brain injury. Factors associated with traumatic brain injury include suspicion for depressed skull fracture and nonfrontal scalp hematoma. Treating clinicians should evaluate and manage delayed presentations outside of the current head injury clinical decision rule parameters because these rules have not been validated for this subset of patients."

POTENTIAL IMPACT: This is the first prospective study to attempt to characterize pediatric patients with delayed presentations to the emergency department following head trauma. Its generalizability is limited by the small number of patients with TBI CT and ciTBI which precluded the use of regression anaylysis and did not allow for the cohort to be divided into less than two years and greater than 2 years are PECARN decision rules.

The impact of the identified predictors of TBI CT and ciTBI on neuroimaging decisions is unclear. Those patients with a suspected depressed skull fracture would very likely have a head CT regardless of the study's results. The predictive ability of a non-frontal scalp hematoma in patients older than 2 years is unclear. Only 1 of the 5 patients over 2 years of age with ciTBI had an isolated non-frontal scalp hematoma.

HEAD TRAUMA:
QUICK BRAIN MRI

In children with and without traumatic brain injury on CT how accurate is a quick brain MRI in identifying those with and without traumatic brain injury?

Nicole Gerber, M.D., Adriana Manikian M.D.
January 2017

Sheridan DC, Newgard CD, Selden NR, Jafri MA, Hansen ML.

QUICK BRAIN MRI FOR THE DETECTION OF ACUTE PEDIATRIC TRAUMATIC BRAIN INJURY.

J Neurosurg Pediatr. 2016 Nov 25:1-6.
PubMed ID: 27885947

STUDY DEFINITIONS

POPULATION	Inclusion: <15 years, present to the level 1 trauma center (primarily or in transfer), initial head CT and underwent qbMRI to follow up head CT. Exclusion: Open neurosurgical procedure before qbMRI, initial head CT images from transferring hospital not available. Setting: Single Children's hospital, 2/2010-12/2013
TEST	QuickBrain MRI (performed on average 24 hours after initial head CT)
REFERENCE STANDARD	Non-contrast head CT Primary Outcome: Traumatic brain injury (TBI) Secondary Outcomes: 1. Clinically important traumatic brain injury (ciTBI), (death, neurosurgical procedure, admission > 48 hours, intubation > 24 hours) 2. Midline shift 3. Characterize lesion as intra-axial or extra-axial.
OUTCOME	Test characteristics
DESIGN	Observational: Retrospective cohort study

HOW SERIOUS WAS THE RISK OF BIAS?

Did participating patients constitute a representative sample of those presenting with a diagnostic dilemma?	Unclear. The authors chose to approach this question with a retrospective cohort study design. In doing so, their patient population was subject to selection bias, as only patients who received both an initial head CT as well as a follow up qbMRI were included in the study. This resulted in a patient population in which there was a very high prevalence of TBI (89%) and ciTBI (63%). This can be compared to the PECARN study which was a prospective study of children presenting with non-trivial head trauma and a Glasgow coma score of ≥ 14 in which only 0.9% had ciTBI.
Did investigators compare the test to an appropriate, independent reference standard?	Yes. Head CT is currently the standard of care for evaluation of pediatric patients with head trauma.
Were those interpreting the test and reference standard blind to the other results?	Yes. The CT and qbMRI images were independently reviewed by two neuroradiology fellows who were blinded to the patient information and to the other MRI and CT results. The radiologists entered the image review information separate from the clinical investigator responsible for the chart review.
Did all patients receive the same reference standard irrespective of the test results?	Yes. In order to be included in the study, the patient's had to have had both an initial head CT as well as a follow up qbMRI.

WHAT ARE THE RESULTS?

WHAT LIKELIHOOD RATIOS WERE ASSOCIATED WITH THE RANGE OF POSSIBLE TEST RESULTS?

		TBI ON CT		
		YES	NO	
TBI ON QUICK BRAIN MRI	YES	41	0	41
	NO	7	6	13
		48	6	54

Primary Outcome: Detection of any TBI
Sensitivity: 41/48 = 85%, 95% CI (73, 93%)
Specificity: 6/6 = 100%, 95% CI (61, 100%).
(6 patients with no TBI on CT had a spinal cord injury)

Note: Likelihood Ratios could not be calculated due to a zero in the calculation.

Note: Predictive values of positive and negative tests could not be calculated. This was not a study of patients with suspected TBI. This was a study of patients with known TBI on head CT (cases) and no TBI on head CT (controls). The ratio of case to controls does not represent the prevalence of TBI in the population.

Secondary Outcomes: ciTBI
Sensitivity: 100%, 95% CI (89, 100%)
Specificity: 100%, 95% CI (34, 100%).

Secondary Outcomes: Midline shift
Sensitivity: 75%, 95% CI (41, 93%)
Specificity: 90%, 95% CI (75, 97%)

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Will the reproducibility of the test results and their interpretation be satisfactory in my clinical setting?	Unclear. The images were reviewed by 2 neuroradiology fellows but interrater reliability (kappa) was not presented. In addition, these were neuroradiology fellows, it would have been helpful to have an attending neuroradiologist participate in the study as well. The neurosurgeon (who was unblinded) was able to identify lesions in most of the studies in which the radiologist did not.
Are the study results applicable to the patients in my practice?	No. (Table 1). A significant number of children were transferred from an outside hospital (82%). Additionally, the study included a very high prevalence of TBI (89%) and ciTBI (63%) and a significant proportion (17%) of children with a Glasgow Coma Scale < 8. This is very different from our population of patients presenting with head trauma and a suspicion of TBI.
Will the test results change my management strategy?	This study has multiple limitations including the small sample size, the time delay between the initial CT and the qbMRI, and the retrospective study design. Most importantly, the study was conducted with a very select, high risk population of patients.
Will patients be better off as a result of the test?	The potential benefits of substituting qbMRI for CT for initial evaluation of head trauma in children is a decrease in radiation exposure. However, with the current test characteristics and the study's limitations qbMRI could not be used as a substitute for CT at this time.

CLINICAL BOTTOM LINE

BACKGROUND: Pediatric head trauma is common. Although the PECARN head trauma rule has helped us to identify children at low risk for clinically important traumatic brain injury (ciTBI) who may not need imaging, a substantial proportion of children undergo CT scanning exposing them to radiation when the vast majority will have negative imaging. The use of a rapid MRI technique would limit radiation exposure and likely decrease the need for sedation compared with traditional MRI.

CLINICAL QUESTION: In children with and without traumatic brain injury on CT how accurate is quick brain MRI (qbMRI) in identifying those with and without traumatic brain injury?

DESIGN/RISK OF BIAS: This was a retrospective cohort study of pediatric patients less than 15 years old presenting to a level 1 pediatric trauma center who had an initial head CT and underwent qbMRI during hospitalization as part of their follow up care. This pilot study included 54 patients of which 89% had a traumatic brain injury on initial CT. There are a number of validity concerns. While the authors state that this was a cohort study it appears to be more of a case-control design with patients with known TBI on head CT representing the cases and those without TBI on head CT serving as the controls (patients with spinal injury). The ratio of case to controls does not represent the prevalence of TBI in the population and predictive values should not be calculated from the study data. Importantly, the qbMRI was obtained on average of 27.5 hours after the initial CT. This time interval may allow for resolution or progression of traumatic brain injury. The indications for the follow up MRI were not specified.

PRIMARY RESULTS: The primary results of this study are that the qbMRI has a sensitivity of 85% 95% CI (73, 93%) and specificity of 100%, 95% CI (61, 100%) for detection of any traumatic brain injury and a sensitivity of 100%, 95% CI (89, 100%) and specificity 100%, 95% CI (34, 100%) for clinically important traumatic brain injury.

APPLICABILITY: This study's results cannot be generalized to the population of children with head trauma with suspected traumatic brain injury. The study included a highly select population of patients requiring follow up imaging. The prevalence of TBI was 89%, with ciTBI of 63%. This is significantly higher than the rate of ciTBI in the population that we would typically consider imaging. For comparison, the PECARN head trauma study reported a prevalence of ciTBI was 0.9% (Kupperman, Lancet, 2009, PubMed ID: 19758692). Additional concerns include the small sample size (54 patients) resulting in very wide confidence intervals for the test characteristics. The interpretation of the diagnostic imaging was performed by neuroradiology fellows instead of attendings, and no kappa was reported to allow assessment of the reproducibility of interpretation of both the CT and qbMRI.

AUTHOR'S CONCLUSION: "This pilot study found that qbMRI has reasonable sensitivity for the identification of pediatric TBI in a cohort of children hospitalized for trauma. Additional work in this area and advances in MRI technology might ultimately validate the qbMRI modality for the initial evaluation of children suspected of having TBI, which would further reduce the risk of their exposure to ionizing radiation."

POTENTIAL IMPACT: This pilot study is a start in addressing the question of the utility of quick brain MRI in children with head trauma. This would significantly reduce a major cause of radiation exposure. Unfortunately, due to the many study limitation, further study is required before qbMRI can be considered a reasonable alternative. Any implementation of qbMRI for patients with head trauma and a suspicion of traumatic brain injury will require collaboration with our pediatric neurosurgery and pediatric radiology colleagues.

HEMORRHAGIC SHOCK: HYPOTENSIVE RESUSCITATION (ADULTS)

In hypotensive adult trauma patients with active hemorrhage, is hypotensive resuscitation with a target systolic blood pressure of 70 mmHg comparable to normotensive resuscitation with a target systolic blood pressure of 100 mmHg in improving in-hospital mortality?

Karen Franco, M.D., Dennis Heon, M.D.
May 2005

Dutton RP, Mackenzie CF, Scalea TM.

HYPOTENSIVE RESUSCITATION DURING ACTIVE HEMORRHAGE: IMPACT ON IN-HOSPITAL MORTALITY.

J Trauma. 2002 Jun;52(6):1141-6.
PubMed ID: 12045644

STUDY DEFINITIONS	
POPULATION	Inclusion: Presented directly from the scene of a traumatic injury, evidence of ongoing hemorrhage, systolic blood pressure SBP < 90 mm Hg recorded at least once within the first hour after injury. Exclusion: Pregnant, central nervous system injury impairing level of consciousness or motor function, > 55 years, medical history of diabetes or coronary artery disease. Setting: Single, Academic Adult Trauma Center, 1996-1999
INTERVENTION	Fluid administration titrated to a “low” systolic blood pressure of 70 mm Hg during the period of active hemorrhage:
CONTROL	Fluid administration titrated to a “conventional” systolic blood pressure of 100 mm Hg during the period of active hemorrhage:
CO-INTERVENTIONS	Blood Pressure Below Target Level: Administration of crystalloid or blood products, to the target systolic blood pressure, maintaining a hematocrit ≥ 25%. Sustained Blood Pressure Above Target Level: Restriction of fluids, administration of appropriate doses of anesthetic or analgesic medication. End of Active Bleeding: Determined by trauma surgeon and anesthesiologist, based on ≥ 1 of the following: 1. Visible control of hemorrhage in the operating room 2. Stable blood pressure not requiring fluid administration for support 3. Tolerance of a normal level of analgesia and sedation 4. Computed tomographic scan or angiography without ongoing hemorrhage. Resuscitation Completed: Followed ATLS guidelines, trauma center protocols. Clinical targets: Normal systolic BP, heart rate, hematocrit > 25%, urine output > 0.5 mL/kg/h, arterial lactate level < 2 mg/dl, and normal arterial base deficit.
OUTCOME	Primary Outcome: In-hospital mortality Secondary Outcome: Duration of active hemorrhage
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Though the method of randomization was not presented.
Was randomization concealed?	Unclear. The article does not state if randomization was concealed.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. There was no significant difference in the number of patients who had surgery, angiography or non-operative management. There was no difference in the percentage of patients with penetrating vs blunt trauma. There was no significant difference in anatomic bleeding site, degree of anatomic injury (ISS) and predicted probability of survival (TRISS).
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Clinicians were aware of group assignment after randomization to determine which clinical pathway to take: achieving hypotension (SBP = 70mmHg) or normotension (SBP >110mmHg). Patients were being resuscitated and probably not aware of the difference aware of treatment allocation. It is unclear if outcome assessors were aware of group allocation. It is unlikely that awareness of group assignment could influence the primary outcome of survival to discharge.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. The primary outcome, in-hospital mortality, was assessed in all patients.
Were patients analyzed in the groups to which they were randomized?	Unclear. There is no mention of an intention to treat analysis though it appears the all patients who entered the study were analyzed in their allocated group.
Was the trial stopped early?	Unclear. The authors do not state that the trial was stopped early. However, a sample size determination was not presented to determine the difference that the authors defined as clinically significant or the sample size required based on this difference.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 110 (55 per group)
Mean age 31 years, 79% male
Penetrating trauma: 48%

Mean (± SD) Systolic BP
Low BP: 100 ± 17 mmHg*
Conventional BP: 114 ± 12 mmHg

*The study never met is target intervention for the “low”
systolic BP of 70 mmHg. No conclusions can be made about the proposed study intervention.

Overall Survival
Low BP: 51/55 = 92.7%
Conventional BP: 51/55 = 92.7%

Duration of Active Hemorrhage
Low BP; 2.97 ± 1.75 hours
Conventional BP: 2.57 ± 1.46 hours

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence intervals were not provided

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	No. The average age in this study was 31 years. 48% sustained penetrating trauma.
Were all patient important outcomes considered?	No. This study only assessed in-hospital mortality and the duration of active hemorrhage. Other potential outcomes could include: long-term morbidity/mortality, neurological sequelae, transfusion requirements and surrogate measures of perfusion such as lactate levels and base deficits.
Are the likely treatment benefits worth the potential harm and costs?	Unclear. Since the study intervention was never achieved it is impossible to assess the risks and benefits of the planned intervention.

CLINICAL BOTTOM LINE

BACKGROUND: Hemorrhage is a leading cause of death in trauma patients. Traditionally, hypotensive patients have been resuscitated with first crystalloid and then packed red blood cells to maintain a normal systolic blood pressure. There have been concerns, supported by animal models, that this approach may increase the rate of hemorrhage due to increased intravascular pressures, lower viscosity and dilution of clotting factors. Theoretically, hypotensive resuscitation may decrease the rate of active hemorrhage and improve clinical outcomes.

CLINICAL QUESTION: In hypotensive adult trauma patients with active hemorrhage, is hypotensive resuscitation with a target systolic blood pressure of 70 mmHg comparable to normotensive resuscitation with a target systolic blood pressure of 100 mm Hg in improving in-hospital mortality?

DESIGN/VALIDITY: This was a single center study in an academic adult trauma center that included 110 patients in the primary analysis. The outcome measures presented were limited to survival to hospital discharge and the duration of active hemorrhage. Other potential outcomes could include: long-term morbidity/mortality, neurological sequelae, transfusion requirements and surrogate measures of perfusion such as lactate levels and base deficits.

PRIMARY RESULTS: Unfortunately, the investigators were unable to achieve the target intervention of a systolic BP of 70mmHg in the hypotensive group. They report an average BP of 100+/-17 mm Hg in the hypotensive group and 114 +/-12 mmHg in the normal group. While this represent a statistically significant difference it is unclear that the difference is a clinically significant one.

APPLICABILITY: The study's results are not generalizable as the study did not attain its target intervention of low systolic blood pressure. In addition, 48% of the patients had sustained penetrating trauma limiting its applicability to populations with a higher proportion of blunt trauma.

AUTHOR'S CONCLUSION: "Deliberate hypotensive management of the actively hemorrhaging trauma patient, as described herein, has no greater impact on mortality than conventional therapy. Further studies in this area should focus on specific patient populations most likely to benefit from deliberate hypotensive resuscitation, and on the development of better markers for assessing tissue perfusion and ischemic risk. Future studies are feasible from the standpoint of emergency consent, but will likely require larger numbers of patients, and therefore multiple investigative sites, to yield clinically relevant results."

POTENTIAL IMPACT: Given the data presented it does not appear that this was a study of hypotensive resuscitation. Even if the target blood pressure were achieved and not adequately reported, there were no clinical or statistically significant differences in the two outcome measures of length of active hemorrhage or overall mortality. Larger clinical trials that can account for important subgroups that contribute to trauma mortality (e.g. penetrating vs blunt injury, significant co-injuries and co-morbidities) and trials that demonstrate both the feasibility and clear efficacy of hypotensive resuscitation are needed before this method of fluid resuscitation can be applied routinely to the hypotensive trauma patient.

HEMORRHAGIC SHOCK: TRANEXAMIC ACID (ADULTS)

In trauma patients with or at risk of significant hemorrhage, what are the effects of the early administration of a short course of Tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusions?

Daniel Silva M.D., Michael Mojica M.D.
June 2010

CRASH-2 trial collaborators.
Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, El-Sayed H, Gogichaishvili T, Gupta S, Herrera J, Hunt B, Iribhogbe P, Izurieta M, Khamis H, Komolafe E, Marrero MA, Mejía-Mantilla J, Miranda J, Morales C, Olaomi O, Olldashi F, Perel P, Peto R, Ramana PV, Ravi RR, Yutthakasemsunt S.

EFFECTS OF TRANEXAMIC ACID ON DEATH, VASCULAR OCCLUSIVE EVENTS, AND BLOOD TRANSFUSION IN TRAUMA PATIENTS WITH SIGNIFICANT HEMORRHAGE: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL (CRASH-2: CLINICAL RANDOMIZATION OF AN ANTIFIBRINOLYTIC IN SIGNIFICANT HEMORRHAGE)

Lancet. 2010 Jul 3;376(9734):23-32.
PubMed ID: 20554319

STUDY DEFINITIONS	
POPULATION	Inclusion: Adult trauma patients with significant hemorrhage (systolic blood pressure < 90 mm Hg or heart rate >110 beats per min, or both), or who were considered to be at risk of significant hemorrhage, and who were within 8 hours of injury Governed by uncertainty principle (unclear indication for Tranexamic acid) Exclusion: Clear indication for Tranexamic acid, Clear indication for not giving Tranexamic acid Setting: Multicenter (40 countries, 274 hospitals), 5/2005-Unknown
INTERVENTION	Loading dose: 1 gram of Tranexamic acid over 10 min, infusion of 1 g over 8 hrs
CONTROL	Matching placebo (0.9% Saline).
OUTCOME	Primary Outcome: Death in hospital within 4 weeks of injury All-cause mortality Cause of death: bleeding, vascular occlusion, multi-organ failure, head injury, other Secondary Outcomes Vascular occlusive events (MI, CVA, PE and DVT) Surgical intervention (neurosurgery, thoracic, abdominal, and pelvic surgery) Receipt of blood transfusion, and units of blood products transfused. Dependency: On Discharge and at day 28 (Modified Oxford Handicap Scale)
DESIGN	Interventional: Randomized clinical trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Randomization was balanced by center, with an allocation sequence based on a block size of eight, generated with a computer random number generator. In hospitals with reliable telephone access, the University of Oxford Clinical Trial Service Unit (CTSU) randomization service was activated. Where telephone access was not available, local pack system that selected the lowest numbered treatment pack from a box containing eight numbered treatment packs used. Randomization was stratified for sex, age, time since injury, blunt vs. penetration trauma, GCS systolic BP, capillary refill and country
Was randomization concealed?	Yes. Tranexamic acid and placebo ampoules were indistinguishable. The treatment packs, also indistinguishable, were prepared by an independent clinical trial supply company. Correct blinding and coding of ampoules was assured by independent random testing of each batch by HPLC to confirm the contents.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. The randomization service used a minimization algorithm balancing for sex, age, time since injury, type of injury (blunt or penetrating), GCS, Systolic BP, respiratory rate, central cap refill time, and country. However, the majority of participants were assigned through the local pack system. Treatment and control groups were similar in all regards, particularly those factors that could affect prognosis, such as age, time from injury, type of injury, admission systolic blood pressure, capillary refill, heart rate and Glasgow Coma Scale.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Participants, site investigators, and trial coordinating center staff were masked to treatment allocation.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Almost complete follow-up in both tranexamic and placebo groups, with 99.7% and 99.5% follow-up, respectively. Only 33 of 10,096 had no follow-up in tranexamic acid group and 47 of 10,115 had no follow-up in placebo group.
Were patients analyzed in the groups to which they were randomized?	Yes. An intention-to-treat analysis was performed (Refer to consort diagram in Figure 1). 0.4% of the patients enrolled in the study were not included in the analysis for various reasons listed on Page 3. For the most part, once the treatment pack number was recorded, the patient was included in the trial whether or not the treatment pack was opened or the allocated treatment started.
Was the trial stopped early	No. The study was not stopped early. An un-blinded interim analysis was performed by independent statistician for ethical reasons to assess for undue harm or benefit.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

	DEATH (ALL-CAUSE)		
	YES	NO	
TRANEXAMIC ACID	1,463	8,630	10,093
PLACEBO	1,613	8,501	10,114
	3,076	17,131	20,207

Primary Outcomes: All Cause Death (See Table 1)
Risk (TXA) = 1,463/10,093 = 14.50%
Risk (Placebo) = 1,613/10,114 = 15.95%
Risk Difference (Placebo-TXA) = 15.95 – 14.50 = 1.45%, 95% CI (0.5, 2.4%)
Relative Risk (TXA/Placebo) = 14.50/15.95 = 0.91,95% CI (0.85-0.97).

Death: Due to Bleeding
Relative Risk (TXA/Placebo) = 0.85 (95% CI 0.76-0.96),

Death: Due to Vascular Occlusion (MI, Stroke, PE)
Relative Risk = 0.69, 95% CI (0.44-1.07)
Not statistically significant (also no difference in death due to multi-organ failure, head trauma or other causes)

Secondary Outcomes (See Table 3)
No statistically significant difference noted: Fatal and non-fatal vascular occlusive events, need for or amount of transfusion and surgery.

Statistically significant decreased in those with no dependency symptoms. TXA (14.7%) Placebo (13.3%)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Given the sample size of over 20,000 patients, the confidence intervals are very narrow (precise). While the confidence intervals for the risk difference and the relative risk of the primary outcome indicate statistical significance, the authors indicate at 2% risk difference or a relative risk of 0.9 to be clinically significant in their sample size determination. The study risk difference was 1.45% and the relative risk was 0.92. Whether a 1.45% difference is clinical significant difference is a matter of judgment.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Somewhat. Inclusion/exclusion criteria and patient characteristics were generally similar to a portion of our trauma population. It should be noted that these criteria were, for the most part, clinical and based on the judgment of the physician orchestrating care in these situations. This is not dissimilar from our ultimate decision making in managing traumatic hemorrhagic shock. However, given the high proportion of mortality in the study population (15.2%) and the percentage of these patients requiring massive transfusion and surgical interventions, the patients in this study appear to have much higher trauma severity scores than those whom we are accustomed to in Lower Manhattan. Nonetheless, given the large number of patients enrolled and wide range health care settings studied, you can argue that findings have a wide range of applicability meeting the study inclusion/exclusion criteria
Were all clinically important outcomes considered?	The primary outcome investigated in this study was death, particularly 28-day all-cause mortality in adult trauma patients with signs of hemorrhagic shock. In this aspect, CRASH-2 revealed a statistically and, arguably, clinically significant reduction of mortality. It also revealed a significant decrease in death due to bleeding. The incidence of fatal and non-fatal vascular occlusive events was also analyzed. No statistically significant difference was noted between TXA and control but the study was not powered to detect any difference in this regard. This study also revealed a statistically significant increase in independency in the TXA group, suggesting that this intervention not only can save lives, but also maintain a semblance of meaningful independent living for survivors. Sub-group analysis also revealed a trend toward a significant reduction of death in patients in whom TXA was administered early and a statistically significant reduction in mortality for patients who were in severe hemorrhagic shock following trauma.
Are the likely treatment benefits worth the potential harm and costs?	Yes. Tranexamic acid is a relatively inexpensive drug without significant side effects, particularly in regards to clotting (although you cannot completely infer that based on this study's analysis). It is associated with a 1.45% reduction in 28-day all-cause mortality giving it an NNT of 67. For every 67 patients treated with TXA 1 additional patient will survive. It is also associated with a 0.8% reduction in mortality from bleeding giving it an NNT of 121. For every 121 patients treated with TXA 1 additional patient not die from bleeding. Tranexamic acid conferred the most benefit in the severe shock group (admission SBP ≤ 75 mm Hg) with an absolute risk reduction of 4.5% (NNT, 22). In summary, based on the findings of this study, the use of Tranexamic acid in trauma patients presenting with suspected hemorrhagic shock, particularly sever shock, is advisable for reducing the risk of death, death by hemorrhage.

CLINICAL BOTTOM LINE

BACKGROUND: Tranexamic acid is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen. Tranexamic acid had been proven efficacious in reducing the need for blood transfusion in surgical patients. Similar benefit should be observed in trauma patients given the similar mechanisms underlying the hemostatic derangements in both.

STUDY QUESTION: In trauma patients with or at risk of significant hemorrhage, what are the effects of the early administration of a short course of Tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusions?

DESIGN/VALIDITY: This was a blinded, randomized clinical trial conducted in a multinational setting inclusive of a wide array of health care settings in almost every continent. Over 20,000 patients were included in the primary intention-to-treat analysis. This is a well-designed study with few major risks of bias. It would have been helpful to provide an injury severity score or serum lactate to compare to the study groups.

PRIMARY RESULTS: Tranexamic acid was shown to have a statistically significant survival benefit when used in trauma patients suspected to have active hemorrhage. The absolute risk of all-cause mortality in the Tranexamic acid group was 14.5% (1,463/10,093). The absolute risk of all-cause mortality in the Placebo group was 15.95% (1,613/10,114). There was a 1.45%, 95% CI (0.5, 2.4%), reduction in all-cause mortality in the Tranexamic acid group. 69 patients would need to be treated with tranexamic acid to prevent 1 additional all-cause death compare to placebo. In addition, there was a statistically significant reduction in death due to bleeding in the Tranexamic acid group. Tranexamic acid (4.9%, 489/10,060), Placebo (5.7%, 574/10,067), Absolute risk difference 0.8%, 95% CI (0.2,1.5%), Relative Risk 0.85, 95% CI (0.76, 0.96). While these differences are statistically significant the clinical significance is unclear. The authors specified a 2% clinical significance in their power analysis. No statistically significant difference was noted for the secondary outcomes of fatal and non-fatal vascular occlusive events, need for or amount of transfusion and need for surgery.

APPLICABILITY: It difficult to determine the characteristics of patients enrolled in this study. Entry was governed by the uncertainty principle. i.e. patients were not included if they had a clear indication or clear contraindication for tranexamic acid potentially resulting in selection bias. While this was a multicenter study, enrollment was predominately low-to-moderate income countries without mature trauma systems. The all-cause mortality rate of 15.3% is considerable above our rate.

AUTHOR'S CONCLUSIONS: "In conclusion, tranexamic acid could be given in a wide range of health-care settings, and safely reduced the risk of death in bleeding trauma patients in our study. The option to use tranexamic acid should be available to doctors treating trauma patients in all countries, and this drug should be considered for inclusion on the WHO List of Essential Medicines. On the basis of these results, tranexamic acid should be considered for use in bleeding trauma patients."

POTENTIAL IMPACT: More objective inclusion criteria are would enhance the studies applicability to our setting. There still exists the concern that this intervention can yield a hypercoagulable state and this study did not include active surveillance for these outcomes was not powered to allay those concerns. Meaningful analysis of this and other secondary outcomes in this study is also limited by survivor bias. Further studies addressing these important outcomes of Tranexamic acid are currently being pursued. Inclusion of Tranexamic acid in our resuscitation protocol, particularly as part of our Massive Transfusion Protocol, should be seriously considered.

HEMORRHAGIC SHOCK: TRANEXAMIC ACID SAFETY

In children <12 years old admitted for trauma and receiving blood products, are those treated with Tranexamic acid (TXA) when compared to those not receiving Tranexamic acid more likely to experience adverse effects (seizures, thromboembolism, renal dysfunction, in-hospital mortality)?

Shweta Iyer, MD; Dennis Heon, MD
January 2019

Maeda T, Michihata N, Sasabuchi Y, Matsui H, Ohnishi Y, Miyata S, Yasunaga H.

SAFETY OF TRANEXAMIC ACID DURING PEDIATRIC TRAUMA: A NATIONWIDE DATABASE STUDY.

Pediatr Crit Care Med. 2018 Dec;19(12):e637-e642
PubMed ID: 30199511

STUDY DEFINITIONS	
POPULATION	Inclusion: 12 years, diagnosis of trauma (see below), received a blood transfusion (packed RBCs, fresh frozen plasma, platelet concentrate, autologous blood transfusion) Trauma sites identified by ICD-10 codes: 1. Head and neck injury 2. Thoracic injury 3. Torso injury (abdomen, lower back, lumbar spine, pelvis, external genitals) 4. Injury to extremities (shoulder, arm, wrist, hip, thigh, foot, knee, and ankle) 5. Multiple injury 6. Injury to unspecified part of trunk, limb, or body region Exclusion: No exclusion criteria were explicitly stated. Sensitivity analysis: Excluded patients not given TXA on day one Setting: Japanese Database including >90% of inpatients discharged from all tertiary care emergency hospitals (>1,000 hospitals nationwide), 7/2010-3/2014
EXPOSURE	Tranexamic acid
NO EXPOSURE	No Tranexamic acid
OUTCOME	Primary Outcomes: Adverse effects of TXA 1. Thromboembolism: myocardial infarction, pulmonary embolism, cerebral infarction, splenic infarction, renal infarction, liver infarction, acute mesenteric hematogenous disorder, arterial embolism, and deep vein thrombosis 2. Seizures: transient convulsive seizures, clonic-tonic convulsions, clonic convulsions, tonic-colonic seizures, and local seizures 3. Renal Dysfunction: requiring renal replacement therapy, including artificial kidney and peritoneal dialysis Secondary outcome: In-hospital mortality
DESIGN	Observational: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	Yes. Propensity score matching was performed to balance the patient backgrounds between the TXA and non-TXA groups. The PS was estimated with a logistic regression model for TXA use as a function of patients' age, gender, body weight, height, trauma sites, hospital type, PICU admission, ambulance transfer, and hospital volume. Additionally, patients were divided into 12 categories which were surrogate markers of health, disease severity, and prior disorders; these as well as operational and surgical variables were used to match patients in the PS design. After a total of 61,779 study patients, patients were matched one-to-one with the closest estimated PS, resulting in 1,914 pairs. The propensity matched groups were quite similar (Table 1)
Were the circumstances and methods for detecting the outcome similar?	Yes. The outcomes were detected by chart review. Since the study is retrospective, the diagnoses were recorded with ICD-10 codes and text in Japanese, including main diagnoses (which is mandatory), comorbidities present at admission, and complications occurring after admission (i.e. the measured outcomes). These data were recorded according to the attending physician's decision.
Was follow-up sufficiently complete?	Not explicitly stated, but follow up seems to be complete since all patients were admitted inpatient. Follow up was until discharge only.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

N = 61,779
TXA: 1,914 (74.2% (1,420/1,914) received TXA on day one)
No TXA: 59,865 (1,914 included in propensity matched analysis)

OUTCOMES: PROPENSITY MATCHED

	NO TXA	TXA	RISK DIFFERENCE (95% CI)
Seizure	0/1,914 (0%)	7/1,914 (0.37%)	0.37% (0.10, 0.64%)
Thromboembolism	2/1,914 (0.1%)	1/1,914 (0.05%)	-0.05% (-0.23, 0.12%)*
Renal Dysfunction	0/1,914 (0%)	3/1,914 (0.16%)	0.16% (-0.02, 0.33%)*
Total Above	2/1,914 (0.1%)	11/1,914 (0.6%)	0.5% (0.1, 0.9%)
In-hospital Mortality	18/1,914 (0.94%)	13/1,914 (0.68%)	-0.26% (-0.83, 0.31%)*

GREEN = Statistically Significant, RED = Not Statistically Significant
*Editor's Note: These confidence intervals were presented incorrectly in Table 2. They do not correspond to the p value and do not include the point estimate. They are recalculated above. Each of the upper limits of the confidence intervals should have been positive.

Sensitivity Analysis: (Including only those who received TXA on 1st day): n = 1,420 pairs
Risk difference (Seizures): (TXA 0.42% - no TXA 0.0%) = 0.42% CI [0.09, 0.76%]

HOW PRECISE IS THE ESTIMATE OF THE RISK?

Confidence intervals for the risk differences are presented above. They are wide.
The CI for the seizure outcome is (0.10, 0.64%)
The CI for the seizure outcome in the sensitivity analysis is (0.09, 0.76%).

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Unclear. It is unclear if the Japanese population is different to the American population in terms of predisposition to hemorrhagic shock after trauma, requiring TXA use. The majority of pediatric trauma was to head and neck whereas in our population the trauma may be predominantly abdominal or extremities.
Was follow-up sufficiently long?	Follow up time is not reported, but the retrospective design seems to include all outcomes due to mandatory diagnosis reporting and length of stay (all patients were admitted). Follow up was complete until discharge. In addition, efficacy outcomes were not reported.
Is the exposure similar to what might occur in my patient?	Yes. In our trauma patients, TXA is part of the pediatric massive transfusion protocol, and is similar to what a patient would require if hemorrhagic shock is a concern.
What is the magnitude of the risk?	There are very few patients who had seizures in the TXA group (7/1914, or 0.37%) and 0/1,914 (0.0%) in the no TXA group. The risk difference of 0.37% indicates that the risk is minimal. Despite being statistically significant it is unclear if this represents a clinically significant difference. Additionally, the risk of adverse outcomes (i.e. seizure) is clinically insignificant as compared to the risk of death from hemorrhagic shock, if TXA is not used.
Are there any benefits that offset the risks associated with exposure?	The benefits of TXA include prevention of blood loss from major trauma; given that this is a life saving measure, the benefits of TXA likely offset the risks of seizure. Additionally, given the limitations of the study, it is not entirely certain that the seizure is directly due to TXA and not due to other factors (or even occurring prior to TXA administration). The number needed to harm for seizures is 270 (1/0.0037). For every 270 patients treated with TXA 1 additional patient would have a seizure compared to those not treated with TXA. Because efficacy outcomes were not provided it is impossible to compare this risk to the benefits of TXA.

CLINICAL BOTTOM LINE

BACKGROUND: Trauma is a life-threatening cause of morbidity and mortality in children. Tranexamic acid (TXA) is an antifibrinolytic agent that has been proven to be effective in adult trauma patients. Prior studies have shown a significant decrease in mortality from bleeding after early administration of TXA in adults (Shakur (CRASH-2), Lancet. 2010, PubMed ID: 20554319). Few studies have been performed in the pediatric trauma population. A recent observational study of 766 injured pediatric patients showed a decrease in mortality and fewer complications in patients treated with TXA (Eckert (PED-TRAX), J Trauma Acute Care Surg, 2014, PubMed ID: 25423534). However, given the small sample size of the study, few conclusions could be drawn regarding safety of TXA.

CLINICAL QUESTION: In children <12 years old admitted for trauma and receiving blood products, are those treated with Tranexamic acid (TXA) when compared to those not receiving Tranexamic acid more likely to experience adverse effects (seizures, thromboembolism, renal dysfunction, in-hospital mortality)?

DESIGN/RISK OF BIAS: This was a well-designed study with minimal risk of bias. The study is a retrospective cohort study that used propensity score matching to include 1,914 pairs of pediatric trauma patients who did or did not receive TXA on day of admission. The study included patients were younger than 12 years with a confirmed diagnosis of trauma (6 categories) and who received a blood transfusion (packed RBCs, fresh frozen plasma, platelet concentrate, and autologous blood transfusion). The primary outcome was rate of adverse events, including thromboembolism, seizures, and renal dysfunction. The secondary outcome was in-hospital mortality. It is interesting that the primary outcome noted is quite rare, while the secondary outcome is of more clinical interest. A sensitivity analysis was also performed to exclude patients who received TXA on 2nd day of admission or later.

There are limitations to this study. There are always possible unobserved and unmatched confounders in an observational retrospective study. Additionally, patients' disease status and medical information was not recorded in detail. The timing of TXA administration was not identified and there is a small chance that patients could have seized prior to the TXA. The indication for TXA, transfusion requirements, and the initiation of a massive transfusion protocol and the efficacy of TXA were not reported.

The initial No TXA group included 59,865 patients. However, only 1,914 (3.2%) were included in the propensity matched analysis. Prior to propensity score matching, it was noted that patients were more likely to receive TXA in certain circumstances (i.e. head/torso injury, ambulance transfer, taller height, larger hospital with more than 400 beds, and academic center hospitals).

PRIMARY RESULTS: Propensity score matching was used to create two equivalent groups comparing TXA to No TXA patients (n =1,914 pairs). Despite the large sample size, adverse effects of TXA were rare occurring in 0.6% of patients in the TXA group and 0.1% in the No TXA group (Risk Difference: 0.5%, 95% CI (0.1, 0.9%). The only statistically significant result was a higher rate of seizures in the TXA group, with a rate of 0.37% (7/1914) in the TXA group and 0.0% (0/1914) in the non-TXA group (Risk difference: 0.37%, 95% CI (0.10, 0.64%). The sensitivity analysis of patients who received TXA on day one included 1,420 pairs. The rate of seizures was also statistically significantly higher in the TXA group (Risk difference: 0.42%, 95% CI (0.09, 0.76) in the sensitivity analysis. Thromboembolism, renal dysfunction, and in-hospital mortality were not statistically significant between the two groups.

OUTCOMES: PROPENSITY MATCHED			
	NO TXA	TXA	RISK DIFFERENCE (95% CI)
Seizure	0/1,914 (0%)	7/1,914 (0.37%)	0.37% (0.10, 0.64%)
Thromboembolism	2/1,914 (0.1%)	1/1,914 (0.05%)	-0.05% (-00.23, 0.12%)
Renal Dysfunction	0/1,914 (0%)	3/1,914 (0.16%)	0.16% (-0.02, 0.33%)
Total Above	2/1,914 (0.1%)	11/1,914 (0.6%)	0.5% (0.1, 0.9%)
In-hospital Mortality	18/1,914 (0.94%)	13/1,914 (0.68%)	-0.26% (-0.83, 0.31%)
GREEN = Statistically Significant, RED = Not Statistically Significant			

APPLICABILITY: This study was performed on the national database in Japan, and had an initial cohort of 61,779 patients. It is unclear if the Japanese population is different to the American population in terms of predisposition to hemorrhagic shock after trauma, requiring TXA use.

The number needed to harm for seizures is 270 (1/0.0037%). For every 270 patients treated with TXA, 1 additional patient would have a seizure compared to those not treated with TXA. Because efficacy outcomes were not provided it is impossible to compare this risk to the benefits of TXA in this study population.

AUTHOR'S CONCLUSION: "Our nationwide study revealed that TXA use on the day of admission for pediatric trauma patients was significantly associated with the occurrence of seizures. Aside from the occurrence of seizure, however, there were no significant differences in other outcomes, including in-hospital mortality, between the TXA and non-TXA groups."

POTENTIAL IMPACT: This study demonstrated a small (0.37%), statistically significant increase in the risk of seizures in the TXA group. Given the small number of patients who experienced adverse outcomes in this study, and the documented benefits of TXA in prior studies, this studies adds evidence to support the use of TXA in pediatric trauma patients. Further studies are needed to depict the timeline of TXA administration to seizure. This topic would benefit from a large multicenter randomized trial of TXA in pediatric trauma patients.

LACERATION REPAIR: ABSORBABLE SUTURES

In patients with trunk or extremity lacerations repaired in the emergency department do absorbable Vicryl Rapide sutures have a comparable cosmetic outcome to non-absorbable Prolene sutures?

Alexis Pankow, M.D., Inna Elikashvili. D.O.
August 2014

Tejani C, Sivitz AB, Rosen MD, Nakanishi AK, Flood RG, Clott MA, Saccone PG, Luck RP.

A COMPARISON OF COSMETIC OUTCOMES OF LACERATIONS ON THE EXTREMITIES AND TRUNK USING ABSORBABLE VERSUS NON-ABSORBABLE SUTURES.

Acad Emerg Med. 2014 Jun;21(6):637-43.
PubMed ID: 25039547

STUDY DEFINITIONS	
POPULATION	Inclusion: Adults and children, linear, small (< 8 cm), minimally contaminated lacerations on the trunk or extremities, Exclusion: Facial lacerations, visible dirt, nonlinear lacerations, bites, significant past medical history, use of daily steroids, wound over area of tension, previous reaction to topical anesthetic Setting: Two urban, adult and pediatric ED's. 5/2010-6/2012
INTERVENTION	Absorbable 4-0 or 5-0 Vicryl Rapide sutures
CONTROL	Non-absorbable 4-0 or 5-0 Prolene sutures
OUTCOME	Primary Outcome Cosmetic appearance: 100-mm validated cosmetic visual analog scale 3 months after repair. Secondary outcomes 1. Infection was determined by patient receiving antibiotics, erythema or tenderness, or purulent material at 10 days post repair wound check. 2. Dehiscence was determined by placement of additional sutures, tissue adhesive or closure by secondary intent. 3. Train tracking (visible suture marks) evaluated at 3 months
DESIGN	Interventional: Randomized clinical trial

ARE THE RESULTS VALID?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized in blocks of 10.
Was randomization concealed?	Yes. Sutures were placed in sealed envelopes and each eligible patient was assigned to the next envelope with one of the two therapeutic interventions.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Table 2 illustrates the demographics of the patients. There was no statistical difference between the 2 groups with regards to age, sex, race, length, number of sutures or number of suture layers. Table1 illustrates the demographics of the patients who were lost to follow up as compared to those who finished the study. Patients lost to follow up were more likely to be male and have longer wounds.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	The plastic surgeons who reviewed the pictures of the repaired lacerations at 3 months post repair were blinded to the type of sutures used. Blinding was not possible for the physician performing the repair as Prolene and Vicryl are different colors and because those in the Prolene group needed instructions to have the sutures removed. It is unlikely that this lack of blinding would influence the secondary outcomes of wound infection, dehiscence or train tracking
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	55 patients were lost to follow up. Patients were advised to return in 10 days for a wound check or suture removal. Phone calls were made for patients who did not return or who chose to have follow-up with their primary care provider. At 3 months post repair, patients were asked to return with a $25 dollar gift card incentive so a picture could be taken of the wound. If the patient could not return a picture sent to the primary investigator was used if it was of good quality. 73 patients (64%) successfully completed all steps of the study (Vicryl = 35, Prolene = 38)
Were patients analyzed in the groups to which they were randomized?	Yes. This was an intention to treat analysis. All patients were analyzed in their original groups without any patient cross over.
Was the trial stopped early	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

Primary Outcome: Wound Cosmesis (Table 3)

SUTURE	N	MEAN VAS (mm)	95% CI
Vicryl Rapide	35	54.1	44.5, 67.0
Prolene	38	54.5	45.7, 66.3
Difference		0.5	

Secondary Outcomes (Table 4)
No significant difference for infections, dehiscence or train tracking.

	COMPLICATIONS		
	YES	NO	
VICRYL RAPIDE	10	25	35
PROLENE	4	34	38
	14	59	73

Risk Vicryl Rapide: 10/35 = 28.5%
Risk Prolene: 4/35 = 10.5%
Risk Difference (V-P) = (28.5% - 10.5%) = 18%, 95% CI (-35.7, 0.3%)
Relative Risk (V/P) = 28.5/10.5 = 2.7, 95% CI (0.94, 7.9)

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Non-inferiority was defined as a difference in VAS as a lower limit for the confidence interval of less than 13 mm. The lower limit of the confidence interval for the mean difference in VAS score did not extend below the 13 mm difference that the authors considered inferior.

The confidence intervals for the absolute risk difference and relative disk of the grouped complications indicate no statistically significant difference between the two suture groups.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Were the study patients similar to my patient?	Patients were ages 6-40 years, mostly African American. Our patients are similar to the mean age of the patients.
Were all clinically important outcomes considered?	Cosmesis and wound complications were considered as outcomes. Patient/parent satisfaction with the cosmetic appearance of the repair would be an additional outcome of interest.
Are the likely treatment benefits worth the potential harm and costs?	Benefits of absorbable sutures include: avoiding the need for a re-visit for suture removal and sparing the anxiety of that procedure in children. There is a decreased cost from fewer visits. Vicryl Rapide is a viable option for patients with extremity or trunk lacerations.

CLINICAL BOTTOM LINE

BACKGROUND: Previous studies have evaluated the use of absorbable sutures on facial lacerations and found that cosmesis is similar for both absorbable and non-absorbable sutures. This study sought to look at the use absorbable sutures on extremity and trunk lacerations in both children and adults. Prolene (non-absorbable) was used as a study control and removed after 10 days. Vicryl Rapide (absorbable) was used as the study intervention. It typically absorbs in 5 -7 days.

CLINICAL QUESTION: In patients with trunk or extremity lacerations repaired in the emergency department do absorbable Vicryl Rapide sutures have a comparable cosmetic outcome to non-absorbable Prolene sutures?

DESIGN/VALIDITY: This was randomized blinded, prospective clinical trial that enrolled 113 patients in the primary analysis. Potential validity concerns of the study include:

1. A high percentage of patients were lost to follow up and who differed from those not lost
2. Lack of standardization of the wound preparation
3. A variety of care givers performing the suturing (attendings, fellows, residents and NP's)
4. Attempted to standardize the photo technique but used some photos sent from patient's phones

PRIMARY OUTCOME: A validated cosmetic visual analog scale was used by plastic surgeons who were blinded to the type of suture that was used to grade the wounds 3 months after the sutures were placed. There was no significant difference between the two groups based on the VAS score. Interestingly the mean score in both groups was approximately 50 mm on a 0-100mm scale. The authors suggest that the possible reason for these low score is that trunk and extremity laceration typically heal more slowly and poorly than facial laceration and that better scores may have be achieved with a 6-month follow-up.

There was also no difference between the groups in complications (infection, dehiscence and train tracking) when assessed individually. When the complications were assessed as a composite variable including any complication, the absolute risk of complication (Vicryl – Prolene) was 18% while the relative risk of complications (Vicryl/Prolene) was 2.7. This may represent a clinical important increase in all complication with Vicryl compared to Prolene. Though there was no statistically significant difference, a larger sample size may have resulted in both statistically and clinically significant increase in all complications.

APPLICABILITY: The patient characteristics were similar to our patient population. Cosmesis and wound complications were considered as outcomes. Patient and/or parent satisfaction with the cosmetic appearance of the repair would be an additional outcome of interest.

AUTHOR'S CONCLUSION: "The use of Vicryl Rapide instead of non-absorbable sutures for the repair of lacerations on the trunk and extremities should be considered by emergency physicians, as it is an alternative that provides a similar cosmetic outcome. However, a larger trial of this type is needed to establish differences between complication rates between the two suture types."

POTENTIAL IMPACT: For patients that are extremely fearful of suture removal or who would prefer to avoid a follow up visit absorbable Vicryl Rapide is an acceptable choice for trunk and extremity laceration closure. Prolene may be a better choice for the avoidance of complications for the majority of patients though additional data on complications would assist in making the decision of absorbable or non-absorbable sutures.

LACERATION REPAIR: ABSORBABLE SUTURES

In children with traumatic lacerations do absorbable plain gut sutures when compared to non-absorbable nylon sutures results in acceptable cosmetic outcomes?

Louis Spina M.D., Adriana Manikian, M.D.
August 2004

Karounis H, Gouin S, Eisman H, Chalut D, Pelletier H, Williams B.

A RANDOMIZED, CONTROLLED TRIAL COMPARING LONG-TERM COSMETIC OUTCOMES OF TRAUMATIC PEDIATRIC LACERATIONS REPAIRED WITH ABSORBABLE PLAIN GUT VERSUS NONABSORBABLE NYLON SUTURES

Acad Emerg Med. 2004 Jul;11(7):730-5.
PubMed ID: 15231459

STUDY DEFINITIONS	
POPULATION	Inclusion: < 18 years, lacerations < 12 hours old, require suturing per recruiting emergency physician Exclusion: Wounds: Animal/human bites, heavily soiled wounds requiring debridement; stellate crush wounds or contaminated puncture wounds, wounds crossing joints or in areas of high tension; lacerations involving tendon, nerve, cartilage or bony injuries, scalp lacerations, could be approximated by tissue adhesives. Patients: History keloid formation, collagen vascular disease, prolonged corticosteroid use, primary/secondary immunodeficiency, type 1 diabetes mellitus, clotting disorders Setting: Single Children's Hospital ED, 1/1999-12/2001
INTERVENTION	Absorbable: Plain catgut sutures (Ethicon)
CONTROL	Non-absorbable: Nylon sutures (Ethicon)
CO-INTERVENTIONS	Standardized Care Plan: Sterile technique, infiltrated with 1% Lidocaine, simple interrupted suturing technique using a cutting needle (5.0 or 6.0 on the face, 4.0 or 5.0 on the Torso/Extremities: 4), 4–5 mm apart, deep layers (if present) closed with plain gut sutures using a buried knot, dry dressing applied and standardized wound care instructions. Steri-strips, topical antibiotics and prophylactic antibiotics at the physician's discretion. Clinic follow-up (Face: 5-7 days, Trunk/Extremity: 7-10 days): Non-absorbable sutures removed. Assessed wound evaluation score (WES), presence of infection, dehiscence Plastic Surgery follow-up (4-5 months): Assessed visual analog scale of cosmesis (VAS), wound evaluation score (WES), scar revision recommendation.
	Primary Outcome: Visual Analog Scale (VAS) of Cosmesis (0-100), 4-5 months Secondary Outcomes Wound Evaluation Score (WES): Assessed at both early and late follow up 1. Presence of step-off 2. Contour irregularities 3. Margin separation 4. Edge inversion 5. Extensive distortion 6. Overall cosmetic appearance. B. Complications 1. Infection: Gross purulent discharge, excessive wound erythema, and/or pain and/or fever. 2. Wound dehiscence. 3. Recommendation for wound revision at 4-5 months.
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized in blocks of 6 to receive absorbable (plain gut sutures) or non-absorbable (Nylon) sutures.
Was randomization concealed?	Unclear. The authors did not specifically state that allocation was concealed but it does not appear that the randomization process could be biased.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. The two groups were similar in age, gender, use of sedation, use of Steri-strips, wound size, mechanism of injury (Table 1), and location of laceration (Table 2). Data on missed patients (Table 3) did not reveal demographic differences from enrolled patients.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	Patients and caregivers were aware of group allocation. Early follow up assessors were not blinded as they were required to know which study group the patient was in to remove non-absorbable sutures. The plastic surgeons at long term follow up were blinded to study group.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	All patients were available for short term follow-up. Only 63/95 (66%) were available for long term follow-up. (similar proportion lost in each groups). Demographic data on those who were lost to long term follow up was similar to patients who were available for follow-up.
Were patients analyzed in the groups to which they were randomized?	Yes. The primary analysis was an intention to treat analysis.
Was the trial stopped early?	No. The trial was not stopped early

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 95, Absorbable = 50, Non-absorbable = 45

Location (Table 2)
Absorbable: 60% face, 20% hand, 10% legs
Non-absorbable: 47% face, 20% hands, 16% legs

Primary Outcome: VAS Score at 4-5 months
VAS Absorbable: 79 mm, 95%, CI (73, 85)
VAS Non-absorbable: 66 mm, 95% CI (55, 76)
Mean Difference: A – NA = 79 – 66 = 13 mm
Neither a p value or confidence interval was reported for this difference. The authors defined a 12-mm difference in VAS score to be clinically significant in their sample size determination.

Optimal Wound Score (WES = 6/6) at 4-5 months
Absorbable: 36%
Non-absorbable: 28%
Relative Risk (NA/A) = 28/36 = 0.88, 95% CI (0.62, 1.26)

Scar Revision Recommended at 4-5 months
Absorbable: 2/34 = 5.9%
Non-absorbable: 1/29 = 3.4%

Short Term Outcomes (n=95/95)

Optimal Wound Score (WES):
Absorbable: 62%
Non-absorbable: 49%
RR (NA/A): 0.73, 95% CI (0.45, 1.17)

Infection: Absorbable 0%, Non-absorbable 2%, p = 0.3
Dehiscence: Absorbable 2%, Non-absorb 11%, p = 0.07

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

See confidence intervals above where provided. The small sample size results in relatively wide (imprecise) confidence intervals

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. Inclusion/exclusion criteria and patient characteristics were appear similar to our ED population.
Were all patient important outcomes considered?	Yes. The primary outcome measure was a previously validated visual analog scale at 4 months after repair. Secondary outcome measures were WES at 5-10 days and at 4-5 months, complications (dehiscence, infection) and need for surgical scare revision. A subgroup analysis on those with face laceration would have been helpful.
Are the likely treatment benefits worth the potential harm and costs?	Wound cosmetic outcome and the secondary outcomes measures appear similar for absorbable and non-absorbable sutures. No appreciable adverse effects were noted. The potential benefit in reducing return visits for suture removal is appealing. NNT = 1/ARD = 1/0.13 = 7.7 For every 7.7 patients treated with absorbable sutures 1 additional patient would have a favorable optimal wound score at 4-5 months.

CLINICAL BOTTOM LINE

BACKGROUND: Operative experience with absorbable sutures for surgically created lacerations has demonstrated good cosmetic outcomes in a variety of surgical fields though evidence is mainly in the form of small case series. The use of absorbable sutures for traumatic lacerations has the benefit of not requiring a follow up visit for suture removal. This is particularly helpful in the screaming toddler who has already gone through one frightening experience to have the wound sutured. This benefit should be measured against the potential for a poor cosmetic outcome.

CLINICAL QUESTION: In children with traumatic lacerations do absorbable plain gut sutures when compared to non-absorbable nylon sutures results in acceptable cosmetic outcomes?

DESIGN/VALIDITY: This was a well-designed randomized clinical trial that included 63 patients in the primary analysis. A visual analog cosmetic score as measured by a blinded plastic surgeon at 4-5 months after wound repair. The only validity concern is that only 66% of patients were available to assess the primary outcome. It may be that those unhappy with their wounds appearance were less likely to follow-up. The authors report that demographic characteristics of those unavailable for follow up were similar to those who remained and that the proportion of those unavailable was the same in each treatment group. The status of who repaired the lacerations was not provided. Were the wounds repaired by attendings, trainees or wound technicians and was this the same in each group?

PRIMARY RESULTS: Plain gut absorbable sutures appeared to have similar cosmetic results in both the short and long term. For the primary outcome of visual analog cosmetic score at 4-5 months the VAS was 79 mm, 95% CI (73, 85) for absorbable sutures and the 6 mm, 95% CI (55, 76) for non-absorbable sutures. The authors do not present a measure of association of the difference (absolute or relative) for this comparison or an indication of its statistical significance. The absolute risk of 13 mm favoring absorbable sutures was greater than the 12 mm difference that the authors considered clinically significant in their sample size determination. There was no statistically significant difference between the two groups in the secondary outcome measures of wound evaluation score at both short and long term follow-up, complications (wound dehiscence and/or infection) of recommendation for scar revision.

APPLICABILITY: The study's results are likely generalizable to those who meet inclusion and exclusion criteria. A sub-analysis of facial wounds, the most common wound location, would have been helpful to determine the impact of these wounds that have the greatest concern for cosmesis as well as the greatest difficulty in suture removal.

AUTHOR'S CONCLUSION: "This prospective study of pediatric patients offers data suggesting that long-term cosmetic outcomes in wounds repaired with simple plain gut sutures seem to be at least as good as in wounds repaired with non-absorbable nylon sutures."

POTENTIAL IMPACT: This small study (n=66 for the primary outcome) supports the use of absorbable sutures for pediatric lacerations. The availability of rapidly dissolving absorbable sutures (such as fast absorbing gut) could potentially improve on the results of this study particularly when applied to patients with low tension lacerations such as those to the face.

TRAUMA PRIMARY SURVEY:
WHOLE BODY VS SELECTIVE CT

In pediatric patients with blunt trauma who undergo CT scanning within 2 hours of ED arrival, is Whole-Body CT (Head, Chest, Abdominal/Pelvis CT) when compared to Selective CT (1-2 CTs) associated with an increased in-hospital survival within 7 days?

Mariju Baluyot, MD., Michael Tunik, MD
December 2018

Meltzer JA, Stone ME Jr, Reddy SH, Silver EJ.

ASSOCIATION OF WHOLE-BODY COMPUTED TOMOGRAPHY WITH MORTALITY RISK IN CHILDREN WITH BLUNT TRAUMA

JAMA Pediatr. 2018 Jun 1;172(6):542-549.
PubMed ID: 29630685

STUDY DEFINITIONS	
POPULATION	Inclusion: 6 months to 14 years of age, history of blunt trauma and received at least one CT scan within the first two hours since ED arrival, admitted or died prior to admission. Exclusion: Transferred from another facility, time of death or hospital discharge not recorded Setting: Multicenter (National Trauma Data Bank), 1/2010-12/2014
EXPOSURE	Whole-body CT: CT head, CT chest and CT abdomen/pelvis scans within the first 2 hours of arrival to ED. This excludes patients too severely injured to go to CT (e.g. those requiring an emergency operative intervention). Cervical spine CT was not included because it is not associated with an ICD9 code and therefore not available in the database
NO EXPOSURE	Selective CT: Those not receiving whole-body CT within the first 2 hours of arrival to ED (1-2 CT scans) This excluded patients of lower acuity that did not require advanced imaging
OUTCOME	Primary Outcome: In-hospital mortality within 7 days after ED arrival. This was chosen to include only those with death directly related to the initial trauma. Secondary Outcomes: ED length of stay, Hospital length of stay
DESIGN	Observation: Retrospective cohort

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)	
DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?	
Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	No. Children who received WBCT were different and often had more severe injuries than those who received selective CT. They were more likely be older, involved in a motor vehicle collision, GCS < 9, hypoxia, hypotension, and require assisted respiration, chest tube, or blood products. They were also less likely to be seen at a university hospital, pediatric trauma center, or largest of pediatric hospitals. Yes. Researchers created propensity scores for each patient (and applied inverse probability weighting) to account for potential confounding in the association of WBCT and mortality, ED length of stay, and total hospital LOS. (See Appendix: Propensity Score Covariates). Table 1 indicates that the known and available prognostic factors were similar after propensity scoring.
Were the circumstances and methods for detecting the outcome similar?	Yes. Both groups of patients were studied retrospectively. All data came from the pediatric trauma database. Since the primary and secondary outcomes were defined during the hospital stay, all data was available.
Was follow-up sufficiently complete?	Yes. The study investigated outcomes for seven days in-hospital after ED arrival.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

Patients: 42,912
Hospitals: 631 (median of 24 patients/hospital)
Whole Body CT: 20.4% (8,757/42,912)
Selective CT: 79.6% (34,155/42,912)
Mortality with 7 days: 0.9% (405/42,912)

Patients with WBCT were:
More likely: Older, GCS < 9, hypoxia, hypotension, assisted ventilation, chest tube, blood products
Less likely: University hospital, pediatric trauma centers, pediatric hospitals with most beds

	Death within 7 days	No death within 7 days	
WBCT	228	8,529	8,757
Selective CT	177	33,978	34,155
	405	42,507	42,912

Primary Outcome: In-hospital mortality within 7 days of ED arrival: Unweighted (Table 1)
Mortality WBCT: 228/8,757 = 2.6%
Mortality Selective CT: 177/34,155 = 0.5%
Absolute Risk Difference: 2.6% – 0.5% = 2.1%, 95% CI (1.7, 2.4%)
Relative Risk: (228/8,575)/(177/34,155) = 5.0, 95% CI (4.1, 6.1)

Primary Outcome: In-hospital mortality within 7 days of ED arrival: Propensity weighted (Table 1))

Mortality WBCT (Adjusted): 1.1% (224/20,992)
Mortality Selective CT (Adjusted): 1.3% (284/21,920)
Absolute Risk Difference (Adjusted): 1.1% - 1.3% = -0.2%, 95% CI (-0.6, 0.1%)
Relative Risk (Adjusted) = 1.1/1.3 = 0.8, 95% CI (0.6, 1.1)

PRIMARY OUTCOME: MORTALITY: OVERALL AND SUBGROUP (TABLE 2)

	WBCT	SELECTIVE CT	RISK DIFFERENCE (95%CI)
Overall (Unadjusted)	2.6%	0.5%	2.1% (1.7, 2.4%)
Overall (Adjusted)	1.1%	1.3%	-0.2% (-0.6, 0.1%)
MVC Pedestrian	2.2%	3.1%	-0.9% (-2.2, 0.3%)
MVC Occupant	2.0%	1.7%	0.3% (-0.4, 1.1%)
GCS < 9	14.9%	14.2%	0.7% (-2.6, 3.9%)
Hypotension	11.9%	10.5%	1.4% (-2.9, 5.8)
Admit to ICU	3.3%	3.6%	-0.3% (-1.2, 0.7)

GREEN = Statistically Significant Difference, RED = Not a Statistically Significant Difference

SECONDARY OUTCOME: MEDIAN ED LOS: OVERALL AND SUBGROUP (TABLE 3)			
	WBCT	SELECTIVE CT	RISK DIFFERENCE (95%CI)
Overall (Unadjusted)	2.7 hours	3.2 hours	-0.5 hours (-0.5, -0.4)
Overall (Adjusted)	2.7 hours	3.1 hours	-0.4 hours (-0.4, -0.3)
MVC Pedestrian	2.6 hours	2.9 hours	-0.3 hours (-0.5, -0.2)
MVC Occupant	3.0 hours	3.2 hours	-0.2 hours (-0.4, -0.1)
GCS < 9	1.4 hours	1.3 hours	0.1 hours (-0.1, 0.2)
Hypotension	1.9 hours	2.3 hours	-0.5 hours (-0.8, -0.1)
Admit to ICU	1.9 hours	2.3 hours	-0.4 hours (-0.9, -0.3)
GREEN = Statistically Significant Difference, RED = Not a Statistically Significant Difference			

SECONDARY OUTCOME: MEDIAN HOSPITAL LOS: OVERALL AND SUBGROUP			
	WBCT	SELECTIVE CT	RISK DIFFERENCE (95%CI)
Overall (Unadjusted)	43.0 hours	22 hours	21.0 hours (19.9, 22.1)
Overall (Adjusted)	41.3 hours	22.4 hours	18.9 hours (16.7, 21.0)
MVC Pedestrian	49.4 hours	29.3 hours	20.1 hours (13.0, 27.3)
MVC Occupant	49.4 hours	26.9 hours	22.5 hours (19.2, 25.8)
GCS < 9	122.4 hours	92.0 hours	30.4 hours (5.0, 55.9)
Hypotension	78.6 hours	30.7 hours	47.9 hours (15.4, 80.3)
Admit to ICU	94.2 hours	68.7 hours	25.5 hours (19.2, 31.8)
GREEN = Statistically Significant Difference, RED = Not a Statistically Significant Difference			

HOW PRECISE IS THE ESTIMATE OF THE RISK?
Primary outcome: In-hospital mortality within 7 days of arrival to ED (Propensity score-weighted) Absolute risk difference (Adjusted): -0.2%, 95% CI (-0.6 to 0.1%) Relative risk (Adjusted): 0.8, 95% CI (0.6 to 1.1) These confidence intervals are fairly narrow due to the large sample size

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Yes. The patients in the trauma registry represent a large variety of practice settings. All patients were admitted so the study results may not apply to those who could be potentially discharged from the ED.
Was follow-up sufficiently long?	Yes. The researchers followed up for the full 7 days of their primary outcome measure.
Is the exposure similar to what might occur in my patient?	Yes. We frequently make clinical decisions regarding risks and benefits of obtaining CT studies in the setting of evaluating pediatric patients who have experienced blunt trauma.
What is the magnitude of the risk?	After propensity score-weighted risk calculations, there was no difference in mortality risk between patients who received WBCT versus Selective CT.
Are there any benefits that offset the risks associated with exposure?	The primary advantage of emergent whole-body CT would be to identify occult injuries sooner and intervene in a timely manner (and potentially decreasing mortality)/ However, this study's results showed do not support a reduction in mortality by WBCT. The potentially to reduce the risk of subsequent malignancies in the pediatric population which are at highest risk with selective CT is encouraging.

CLINICAL BOTTOM LINE

BACKGROUND: Computed tomography (CT) has been used in the evaluation of patients who have experienced blunt trauma as a means of detecting injuries and guiding management in the ED and hospital setting. Obtaining CT images of multiple areas of the body, or whole-body CTs (WBCTs), in the setting of severe trauma in adults has been shown in some studies to improve mortality as occult injuries are detected more rapidly. However, those caring for children must always take into consideration the risks and benefits of radiation exposure as children are more sensitive to radiation and more at risk of developing cancer in the future than adults. With trauma as the leading cause of death among children in the US, it is important to be able to utilize our resources appropriately to make accurate, prompt, and safe decisions in regards to trauma-related injuries in children.

CLINICAL QUESTION: In pediatric patients with blunt trauma who undergo CT scanning within 2 hours of ED arrival, is Whole-Body CT (Head, Chest, Abdominal/Pelvis CT) when compared to Selective CT (1-2 CTs) associated with an increased in-hospital survival within 7 days?

DESIGN/RISK OF BIAS: This was a well-designed, multicenter, retrospective cohort study utilizing data from the National Trauma Data Bank. Those who received WBCT were compared to those receiving selective CT within 2 hours of ED arrival. Cervical spine CT scans were excluded from the analysis because this data was not available. The primary outcome was in-hospital mortality within 7 days of ED arrival. However, neither the indications or the results of the CT scans are presented. Potential benefits of CT scans other than an effect on mortality were not addressed. These benefits include identifying injuries requiring intervention and identifying patients requiring a higher level of care (e.g. PICU admission) or re-imaging to ensure lack of injury progression or injury resolution.

PRIMARY RESULTS: 42,912 patients cared for at 631 hospitals were included in the analysis. WBCT was utilized in 20.4% and Selective CT in the remaining 79.6%. The overall in-hospital mortality within 7 days of ED arrival was 0.9%. Patients undergoing WBCT had different characteristics and are generally sicker than children who received selective CT. However, the two study groups were similar after propensity scoring.

After propensity-weighting, there was no significant difference in mortality in children who experienced blunt trauma and received WBCT or selective CT. The absolute risk difference was -0.2%, 95% CI (0.6 to 0.1%) and the relative risk was 0.8, 95% CI (0.6, 1.1). This lack of difference in mortality between the two groups was seen even with consideration of how the child was injured (pedestrian, MVC occupant) or how sick the child was in the ED (GCS <9, hypotension, ICU admission).

The WBCT group had overall shorter LOS in the ED (by about half an hour). This difference is not clinically significant. Hospital LOS in the WBCT group (41.3 hours) was statistically significant longer than the selective CT group (22.4 hours) (Risk Difference 18.9 hours (16.7, 21.0). Similar increases were seen in subgroups based on the mechanism of injury (pedestrian, MVC occupant) r and illness severity (GCS <9, hypotension, ICU admission). The clinical significance of the approximately 19 hours difference in hospital length is unclear.

PRIMARY OUTCOME: MORTALITY: OVERALL AND SUBGROUP (TABLE 2)			
	WBCT	SELECTIVE CT	RISK DIFFERENCE (95%CI)
Overall (Unadjusted)	2.6%	0.5%	2.1% (1.7, 2.4%)
Overall (Adjusted)	1.1%	1.3%	-0.2% (-0.6, 0.1%)
MVC Pedestrian	2.2%	3.1%	-0.9% (-2.2, 0.3%)
MVC Occupant	2.0%	1.7%	0.3% (-0.4, 1.1%)
GCS < 9	14.9%	14.2%	0.7% (-2.6, 3.9%)
Hypotension	11.9%	10.5%	1.4% (-2.9, 5.8)
Admit to ICU	3.3%	3.6%	-0.3% (-1.2, 0.7)
GREEN = Statistically Significant Difference, RED = Not a Statistically Significant Difference			

APPLICABILITY: The large number patients in the trauma registry represent a large variety of practice settings. The study's results are likely generalizable to pediatric blunt trauma patients meeting the studies inclusion and exclusion criteria. The study excluded those not admitted and those not requiring a CT so the study results may not apply to those who could be potentially discharged from the ED.

AUTHOR'S CONCLUSION: "In this large, multicenter, propensity-weighted study of children with blunt trauma, emergent WBCT was not associated with lower mortality for children with blunt trauma, compared with a selective CT approach. This outcome was consistent regardless of how severely injured the children were. These results have implications for how emergency and trauma specialists care for injured children. Although WBCT may provide more information about the injured child, that information does not appear to be lifesaving. With growing concerns regarding excessive radiation exposure for injured children, physicians should attempt to limit CT exposure whenever possible."

POTENTIAL IMPACT: This large multicenter study did not demonstrate a difference in in-hospital mortality within 7 days of ED arrival in pediatric blunt trauma patients undergoing Whole Body CT compared to Selective CT. This data support selective CT scanning in order to limit unnecessary radiation exposure in the pediatric population as children are at the higher risk of developing cancer in the future. However, neither the indications or the results of the CT scans were presented. Potential benefits of CT scans other than an effect on mortality were not addressed. These benefits include identifying injuries requiring intervention and identifying patients requiring a higher level of care (e.g. PICU admission) or re-imaging to ensure lack of injury progression or injury resolution.

APPENDIX: PROPENSITY SCORING COVARIATES	
Age	Assisted ventilation
Sex	Transfusion: PRBC, FFP, platelets
Race	Chest Tube
Mechanism of injury	Hospital region
Payment type	Adult trauma center status
Glasgow Coma Score	Pediatric trauma center status
Hypoxia	Number of pediatric beds
Hypotension	

VASCULAR ACCESS

1. Peripheral: Ultrasound Guided IV: Annals EM 2019

PERIPHERAL VENOUS ACESS: ULTRASOUND GUIDED

In pediatric patients with difficult intravenous access does ultrasound guidance improve the first attempt success rate compared to traditional peripheral intravenous insertion technique?

Michael Mojica, MD
August 2019

Vinograd AM, Chen AE, Woodford AL, Fesnak S, Gaines S, Elci OU, Zorc JJ.

ULTRASONOGRAPHIC GUIDANCE TO IMPROVE FIRST-ATTEMPT SUCCESS IN CHILDREN WITH PREDICTED DIFFICULT INTRAVENOUS ACCESS IN THE EMERGENCY DEPARTMENT: A RANDOMIZED CONTROLLED TRIAL.

Ann Emerg Med. 2019 Jul;74(1):19-27.
PubMed ID: 31126618

STUDY DEFINITIONS	
POPULATION	Inclusion: 0-18 years (Subgroups: 0-3 years, > 3 years) Required intravenous access Pediatric difficult intravenous access (DIVA) score ≥ 3 (See appendix) Exclusion: Critically ill requiring emergency intravenous access Prior IV access during current visit Parent/guardian did not speak English Setting: Single Children's Hospital (US), 6/2014-12/2016
INTERVENTION	Ultrasound Guided Peripheral Intravenous Access (USPIV) Performed by 1 of 18 trained caregivers when available Required ≥ 10 Successful supervised ultrasound-guided peripheral IV placed Training: Attending: Self-taught (1) Attending (2) / Fellow (10): Fellowship ultrasound rotation with USPIV Nurses (5): 4 hours didactic and hands-on training Technique: Single operator Dynamic technique in short access (vein visualization during placement) Probe in transverse position Angiocath gauge and length at user discretion (encouraged to use longer)
CONTROL	Traditional Peripheral Intravenous Access (TPIV) Performed by a senior nurse (>3 years of training) Angiocath gauge and length at user discretion Could utilize transillumination and/or heat packs
CO-INTERVENTIONS	If IV access was not successful the care team determined the next approach 1. Same method 2. Alternative method 3. Consult IV line team 4. Consider alternatives to IV placement
OUTCOME	Primary Outcome: First Attempt Success Rate Secondary Outcomes: 1. Number of IV access attempts 2. Time to IV Placement (Randomization → IV flush without extravasation) 3. IV Survival: IV flush → Removal (excluded removal if no longer needed) 4. Complications: Phlebitis, infiltration, line occlusion, bleeding, leaking, pain, dislodgement 5. Parent Satisfaction: 1(worst)→10(best). Assessed after placement or no decision made to make no further attempts
DESIGN	Interventional: Randomized Clinical Trial

HOW SERIOUS WAS THE RISK OF BIAS?	
DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?	
Were patients randomized?	Yes. Patients were randomized in permuted groups. Randomization was stratified by age (0-3 years, > 3 years).
Was randomization concealed?	Yes. Randomized utilized sealed envelopes. It does not appear the allocation could be biased.
Were patients in the study groups similar with respect to known prognostic factors?	Yes (Table 1). Patients were similar with regard to age, sex, race and ethnicity. The mean DIVA score in each group was not reported. A DIVA score of ≥ 3 was required for inclusion. However, the maximum score for those < 1 years of age is 11, for those > 1-3 years of age is 9 and for those > 3 years is 8.
WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	After concealment allocation, the study was not blinded. Providers and parents were aware of the treatment group. It is unclear, if those assessing the duration of placement outcome were blinded to study group.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. The primary outcome and many of the secondary outcomes were available in the ED. Only 85% of those admitted had a documented time of removal.
Were patients analyzed in the groups to which they were randomized?	Yes. An intention to treat analysis was completed for the primary outcome.
Was the trial stopped early?	Yes. The trial was stopped early when more nurses were trained and USPIV became the standard of care for patients with difficult intravenous access. A sample size of 93 patients per group (186 total) was initially calculated based on a 20% difference in the primary outcome. 165 patients were included in the final analysis and the 39.6% higher first attempt success rate in the USPIV group was statistically significant indicating sufficient power to find a difference with the smaller sample size.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N=167 randomized (165 included in the analysis)
USPIV = 82, TPIV = 83
< 3 years = 99, > 3 years = 66
TPIV: 56 nurses, USPIV: 17 providers
USPIV Provider Success Rate: Attending (n=3): 100%, RN (n=3): 91%, Fellow (n=10): 74%

PRIMARY OUTCOME: FIRST ATTEMPT SUCCESS

	0-3 YEARS	> 3 YEARS	TOTAL
Traditional PIV	46.0% (23/50)	45.5% (15/33)	45.8% (38/83)
Ultrasound Guided PIV	81.6% (40/49)	90.9% (30/33)	85.4% (70/82)
Relative Risk (95% CI)*	1.8 (1.3, 2.5)	2.0 (1.4, 3.0)	1.9 (1.5, 2.4)
Risk Difference (95% CI)*	35.6% (16.8, 51.1%)	45.5% (23.5, 62.2%)	39.6% (25.5, 51.5%)

GREEN = Statistically Significant, RED = Not Statistically Significant
*Relative Risk = USPIV/TPIV, Risk Difference = USPIV - TPIV
Relative Risk and Risk Difference Calculated at: CENTRE FOR EBM WEBSITE

SECONDARY OUTCOMES

	USPIV	TPIV	RD or RR*
# Attempts (median)	1, IQR (1,1)	2, IQR (1,2)	1, 95% CI (0.8, 1.2)
Time to Placement (min)	14, IQR (13, 15)	28, IQR (21, 31)	Not Presented
Duration (days) (95% CI)	7.3 (3.7, 9.5)	2.3 (1.8, 3.3)	Not Presented
Parent Satisfaction (1-10)	10, IQR (8,10)	8, IQR (5,10)	2, 95% CI (0.9, 3.1)
Complications (%)(95% CI)	40% (30, 53.5%)	48% (34, 66.5%)	0.84 (0.53, 1.34)

GREEN = Statistically Significant, RED = Not Statistically Significant
*Relative Risk and Risk Difference

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

Confidence intervals for the relative risks, risk difference and median differences are included above.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Yes. Patients are likely typical of those presenting to the ED. The median age was 2.1 years in both groups. Patients with difficult intravenous access due to complex medical problems are likely to present more frequently to the emergency department of a children's hospital.
Were all patient important outcomes considered?	Yes. The study assessed a primary outcome and multiple secondary outcomes that a relevant to clinical care and included an assessment of parental satisfaction.
Are the likely treatment benefits worth the potential harm and costs?	The was a statistical and clinically significant improvement in the USPIV group with difficult intravenous access (Risk Difference: USPIV – TPIV = 85.4% - 45.8% = 39.6%, 95% CI (25.5, 51.5%). This corresponds to a NNT = 2.5 (1/0.396). For every 2.5 patients for which USPIV is used, 1 additional patient will have a successful IV placed on the first attempt compared to TPIV.

CLINICAL BOTTOM LINE

BACKGROUND: Obtaining peripheral venous access in children is difficult. This is particularly true for infants and toddlers and those with chronic medical conditions requiring frequent intravenous access. Traditional intravenous placement is associated with an overall 75% first attempt success rate but only 50% of the with difficult venous access (Curtis, CMAJ 2015, PubMed ID: 25897047).
A pediatric Difficult Intravenous Access (DIVA) Score of greater than 4 is associated with a 50% first attempt success rate (Yen K, Pediatr Emerg Care. 2008, PubMed ID: 18347490). Ultrasound allows for direct visualization and cannulation of the vein and could decrease the number of peripheral venous access attempts and the need for more invasive venous access such as intraosseous access and central venous lines.

CLINICAL QUESTION: In pediatric patients with difficult intravenous access does ultrasound guidance improve the first attempt success rate compared to traditional peripheral intravenous insertion technique?

DESIGN/VALIDITY: This was a well-designed single-center randomized clinical trial. The study randomized those with a difficult intravenous access score of ≥ 3 to traditional peripheral intravenous access (TPIV) or ultrasound guided peripheral intravenous access (USPIV). Randomization was stratified by age (< 3 years and > 3 years). Patients were enrolled as a convenience sample when those with USPIV training were available. Providers included attendings, fellows and nurses with differing training but all had to complete at least 10 successful supervised USPIV. Technique after first attempt failure was at the discretion of the provider as was the gauge and length of the intravenous catheter. Providers and parents were not blind to the study interventions. This could potentially bias the parental satisfaction outcome. Study groups were similar with regard to age, gender, race and ethnicity. The median DIVA score for each group was not reported. The primary outcome was first attempt success rate. Secondary outcomes included the number of attempts made, duration to completion, duration of catheter utility, complications and parent satisfaction.

The trial was stopped early when more nurses were trained and ultrasound guided peripheral intravenous approach became the standard of care. A sample size of 93 patients per group (186 total) was calculated based on a 20% difference in the primary outcome. 165 patients were included in the final analysis and the 39.6% higher first attempt success rate in the USPIV group was statistically significant indicating sufficient power to find a difference with the smaller sample size.

PRIMARY RESULTS: 165 patients were included in the primary intention to treat analysis. There was a statistical and clinically significant improvement in first attempt success using USPIV in patients with difficult intravenous access (Risk Difference: USPIV – TPIV = 85.4% - 45.8% = 39.6%, 95% CI (25.5, 51.5%). This difference was also significant in both of the age categories.

PRIMARY OUTCOME: FIRST ATTEMPT SUCCESS			
	0-3 YEARS	> 3 YEARS	TOTAL
Traditional PIV	46.0% (23/50)	45.5% (15/33)	45.8% (38/83)
Ultrasound Guided PIV	81.6% (40/49)	90.9% (30/33)	85.4% (70/82)
Relative Risk (95% CI)*	1.8 (1.3, 2.5)	2.0 (1.4, 3.0)	1.9 (1.5, 2.4)
Risk Difference (95% CI)*	35.6% (16.8, 51.1%)	45.5% (23.5, 62.2%)	39.6% (25.5, 51.5%)
GREEN = Statistically Significant, RED = Not Statistically Significant *Relative Risk = USPIV/TPIV, Risk Difference = USPIV - TPIV Relative Risk and Risk Difference Calculated at: CENTRE FOR EBM WEBSITE			

USPIV results in statistically few attempts, a shorter time to placement, longer duration of IV placement in admitted patient, an increase in parent satisfaction without a higher rate of complications.

SECONDARY OUTCOMES			
	USPIV	TPIV	RD or RR*
# Attempts (median)	1, IQR (1,1)	2, IQR (1,2)	1, 95% CI (0.8, 1.2)
Time to Placement (min)	14, IQR (13, 15)	28, IQR (21, 31)	Not Presented
Duration (days) (95% CI)	7.3 (3.7, 9.5)	2.3 (1.8, 3.3)	Not Presented
Parent Satisfaction (1-10)	10, IQR (8,10)	8, IQR (5,10)	2, 95% CI (0.9, 3.1)
Complications (%)(95% CI)	40% (30, 53.5%)	48% (34, 66.5%)	0.84 (0.53, 1.34)
GREEN = Statistically Significant, RED = Not Statistically Significant *Relative Risk and Risk Difference			

APPLICABILITY: The study's results can likely be generalized to patients meeting its inclusion and exclusion criteria in a similar setting. The main concern is in defining the training and experiences necessary to become competent at USPIV and to maintain those skills. The success rate of providers difference by their status (Attending: 100%, RN: 91%, Fellow: 74%). The first attempt success risk difference (in favor of the USPIV group) was 39.6%, 95% CI (25.5, 51.5%). This corresponds to a NNT = 2.5 (1/0.396). For every 2.5 patients for which USPIV is used, 1 additional patient will have a successful IV placed on the first attempt compared to TPIV.

AUTHOR'S CONCLUSION: "In summary, in our randomized trial, ultrasonographically guided intravenous line placement in children with predicted difficult intravenous access by experienced providers improved first-attempt success rates, reduced the time to placement, and decreased the overall number of attempts. Furthermore, ultrasonographically guided intravenous lines lasted longer and were not found to cause more complications than traditional ones. Parental and patient satisfaction were significantly higher for patients randomized to the ultrasonographically guided intravenous line group. These results may be used to update guidelines for intravenous line access in children in an effort to limit the number of needlesticks they experience."

POTENTIAL IMPACT: Ultrasound guided peripheral intravenous placement should be the preferred technique in pediatric patients with predicted difficult intravenous access. USPIV had a higher first attempt success rate, fewer required attempts, a shorter time to placement, an increased line longevity and higher parent satisfaction without a corresponding increase in the complications when compared to traditional peripheral intravenous insertion. This study included trained and certified proceduralists. The extent of didactic and hands-on training required to develop competence at USPIV and to maintain those skills in unclear.

APPENDIX: PEDIATRIC DIVA SCORE

PEDIATRIC DIFFICULT INTRAVENOUS ACCESS (DIVA) SCORE			
Vein Visibility	Visible = 0		Not Visible = 2
Vein Palpability	Palpable = 0		Not palpable = 2
Age	≥ 36 months = 0	12-35 months = 1	< 12 months = 3
Prematurity	NO = 0		YES = 3
Skin Shade	Light = 0	Dark = 1	
Range: 0-11, A score of 4 or more had a more than 50% likelihood of first attempt failure			

Yen K, Riegert A, Gorelick MH.
Derivation of the DIVA Score: A Clinical Prediction Rule for the Identification of Children with Difficult Intravenous Access.
Pediatr Emerg Care. 2008 Mar;24(3):143-7., PubMed ID: 18347490