Pediatric Respiratory Disease: 
A Model for the Future of Emergency Medicine Research

Joseph J. Zorc, MD, MSCE
Mark Fishman Professor, Department of Pediatrics
Perelman School of Medicine, University of Pennsylvania
Director, Emergency Information Systems
The Children’s Hospital of Philadelphia
Disclosures

Financial: No interests to disclose

Professional: Academic medicine career

• Intervenational research in respiratory illness
  • Randomized trials in asthma / bronchiolitis
  • NHLBI K 23 Award
  • American Academy of Pediatrics (AAP) & PECARN multicenter research
  • AAP Bronchiolitis Guideline
  • Formal Quality Improvement training at Intermountain Health Care

• Information Technology
  • Initially administrative role, ED tracking system
  • Implemented full EHR functionality gradually over 15 years
  • Clinical Informatics Board Certification
  • Teaching and involvement in CHOP Clinical Informatics fellowship
Top 5 Reasons to Become an Emergency Medicine Researcher

1.

2.

3.

4.

5.
Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis

**Diagnosis**
- Bronchiolitis refers to bronchiolitis obliterans and lower respiratory illness.

**Recommendations**
- **Bronchiolitis:**
  - Diagnosis should be based on clinical features.
  - Treatment is symptomatic.

**Asthma**
- Asthma is a chronic inflammatory disease of the airways.
- Key features:
  - Airway hyperresponsiveness.
  - Variable airflow obstruction.
- Management involves:
  - Avoiding triggers.
  - Using inhaled corticosteroids.
  - Inhaled long-acting beta agonists.

**Graphs**
- *Transit Early Wheezers vs. Non-Atopic Wheezers vs. IgE-Associated Wheezes/Asthma*
- *PHOENIX trial 4-class model* (N=3748)
- *ALSPAC trial 6-class model* (N=11,740)
Top 5 Reasons to Become an EM Researcher

5. New opportunities to translate evidence effectively
c/o Ted Eyton http://www.flickr.com/photos/taedc/sets/72157633347033275/
Promise of IT to improve healthcare

Health IT’s failure to quickly deliver on its promise is not due to its lack of potential but to shortcomings in the design and implementation of health IT systems…

Ultimately, there is only so much that the government and vendors can do. Providers must do their part by reengineering existing processes of care to take full advantage of the efficiencies offered by Health IT

Arthur Kellerman, Health Affairs 2013
Mild-Moderate asthma in the CHOP ED
Problem: Overtreatment with neb instead of MDI

- Evidence review showed benefit of MDI
- Multi-disciplinary review / Process analysis
  - Key Driver: MD/NPs reluctant to order MDI: Concern about reassessment
  - Duplicated resources: MDI given at discharge
  - Measurements: MDI use, length of stay, admissions

Evidence for reduced length of stay
Trend towards reduced admissions
Problem:
• Overtreatment of mild-moderate patients
• MDI instead of neb reduces length of stay / costs

Intervention:
• Order set modification
• Explicit options based on triage level
• Mild-moderate (ESI Triage 3/4): MDI puffs q20 x 3
• Conditional order: Respiratory to stop when improved

Goal:
• Increase % of ESI 3 /4 pts discharged in < 3 hrs by 10% within 3 months
ED Pathway for Evaluation/Treatment of Children with Asthma

**Goals and Metrics**

**Child with Asthma and Respiratory Complaint**

**Triage (Critical/Acute/Urgent)**

**MD/CRNP/RN Brief Rapid Assessment**

**Determine Severity Level of Asthma Exacerbation**

**Mild: ESI Triage 4**
- Consider Dexamethasone tablet (alternative prednisone/olone)
- If needed: Albuterol MDI - 2-4 puffs
- MDI spacer teaching

**Moderate: ESI Triage 3**
- Dexamethasone tablet (alternative prednisone/olone)
- Albuterol MDI q20min x 3, prn RT assess

**Severe: ESI Triage 1-2**
- Prednisone/olone/Methylpred
- Unineb: Albuterol x3 + ipratropium
- Critical: consider SQ terb

**Assess** after completion of β-agonist

**Considerations for further diagnostic testing**
- Very explicit instructions and indications

### Embedded order panel

**Order Sets**

#### ED Asthma Pathway

**ED Asthma Pathway: Pharmacy**

- **Steroids:** Order on arrival if not responding to home treatment
- **Mild Bronchodilator (ESI 4, Minimal/NoWOB):** Administer 2-4 puffs if needed and place orders for discharge teaching/prescriptions
- **Moderate Bronchodilator (ESI 3, Mild WOB):** Administer puffs, RT to reassess and repeat prn, observe 1 hour after treatment prior to discharge
  - albuterol inhaler 4 puffs, 5-10kg
- **Severe Bronchodilator (ESI 1/2, Mod-Severe WOB):** Administer albuterol/ipratropium via unineb over 1 hour, observe 1-2 hours prior to discharge
- **Poor response to initial therapy (Mod-Severe WOB):** Repeat unineb, consider IV Mg with NS bolus
- **Severe without response:** Continuous albuterol, place IV. Consider IV terbutaline bolus after IV Mg if admitted to ICU

**Smoking Cessation Education**

*Please provide ED smoking cessation education.*

**Asthma Discharge Teaching**
ESI Triage 3-4 Discharged Patients
% Use of 1 hr continuous neb

Pathway change

Zorc et al. AAP NCE 2016

20% decrease in admissions
## Bronchodilator effect on clinical score for bronchiolitis

**Gadomski, Cochrane Reviews 2014**

### Inpatient

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Bronchodilator N</th>
<th>Mean(LOD)</th>
<th>Placebo N</th>
<th>Mean(LOD)</th>
<th>Std Mean Difference (95% CI)</th>
<th>P (trend)</th>
<th>Std Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Inpatient studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadomski 1997</td>
<td>18</td>
<td>4.3 (3.6)</td>
<td>22</td>
<td>4.1 (0.6)</td>
<td>0.17 (0.17, 0.61)</td>
<td>0.13</td>
<td>0.2 (0.08, 0.53)</td>
</tr>
<tr>
<td>Gotshalk 2004</td>
<td>16</td>
<td>4.5 (0.8)</td>
<td>29</td>
<td>4.1 (0.8)</td>
<td>-0.4 (0.02, 0.75)</td>
<td>0.09</td>
<td>-0.3 (0.01, 0.61)</td>
</tr>
<tr>
<td>Karadag 2005 - I</td>
<td>18</td>
<td>4.2 (0.6)</td>
<td>22</td>
<td>4.4 (1.9)</td>
<td>0.17 (0.01, 0.39)</td>
<td>0.04</td>
<td>0.2 (0.05, 0.32)</td>
</tr>
<tr>
<td>Karadag 2005 - II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karadag 2005 - III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Outpatient

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Bronchodilator N</th>
<th>Mean(LOD)</th>
<th>Placebo N</th>
<th>Mean(LOD)</th>
<th>Std Mean Difference (95% CI)</th>
<th>P (trend)</th>
<th>Std Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2 Outpatient studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alonso 2012</td>
<td>17</td>
<td>3.7 (0.4)</td>
<td>20</td>
<td>3.7 (0.3)</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.99</td>
<td>0.0 (0.0, 0.0)</td>
</tr>
<tr>
<td>Amini 2010 I 0%</td>
<td>31</td>
<td>3.5 (0.2)</td>
<td>30</td>
<td>3.6 (0.3)</td>
<td>-0.12 (0.09, 0.27)</td>
<td>0.32</td>
<td>-0.1 (0.09, 0.27)</td>
</tr>
<tr>
<td>Amini 2010 I 1%</td>
<td>36</td>
<td>3.5 (0.2)</td>
<td>30</td>
<td>3.6 (0.3)</td>
<td>-0.12 (0.09, 0.27)</td>
<td>0.32</td>
<td>-0.1 (0.09, 0.27)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**: -0.30 [-0.54, -0.05]
Clinicians should not administer albuterol to infants and children with a diagnosis of bronchiolitis (Evidence Quality: B; Recommendation Strength: Strong Recommendation).
EDITORIAL


Paul Walsh, MD, MSc†
Stephen J. Rothenberg, PhD‡

†University of California, Davis, Department of Emergency Medicine, Davis, California
‡Sutter Medical Centers of Sacramento, Pediatric Emergency Medicine, Sacramento, California
§Instituto Nacional de Salud Pública, Centro de Investigación en Salud Poblacional, Cuernavaca, Morelos, Mexico

Supervising Section Editor: Mark I. Langdorf, MD, MHPE
Submission history: Submitted December 4, 2015; Accepted January 6, 2015
Electronically published January 12, 2015
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2015.1.24930
Subject: My name is Dr. Indigo Montoya, You Killed Albuterol..

... prepare to die.

In face of the recent... will be endorsing this... Our center will serve therapy for the treat... It is my hypothesis th... I anxiously await the...
N=24, 1st episode of bronchiolitis, sedated with chloral hydrate

No significant change in score or PFTs with albuterol (salbutamol)

Sanchez et al. Journal of Pediatrics, 1993
Sanchez et al. Journal of Pediatrics, 1993

Albuterol

Racemic Epinephrine
“Do Not Order” Set

No change in admission, LOS, revisits
Key to effective care for asthma and bronchiolitis
Top 5 Reasons to Become an EM Researcher

4. Build a career in academic medicine

5. New opportunities to translate evidence effectively
Systemic steroids for acute asthma: Cochrane meta-analysis

Pediatric studies
- Storr 1987
- Tal 1990
- Scarfone 1993
- Connett 1994a
- Connett 1994b
- Wolfson 1994

Total

Steroids better: OR = 0.4 (0.3 - 0.7)
No steroids better

Odds Ratio for hospitalization

Rowe et al. Cochrane Database 2005
Triage Nurse Initiation of Corticosteroids in Pediatric Asthma Is Associated With Improved Emergency Department Efficiency

AUTHORS: Roger Zemek, MD, Amy Plint, MD, MSc, Martin H. Osmond, MD, CM, Tom Kovesa, MD, Rhonda Darrell, BScN, Nicholas Perrin, and Nick Barrowman, PhD

WHAT'S KNOWN ON THIS SUBJECT: Early administration of oral corticosteroids is essential for children presenting to emergency departments with moderate to severe acute asthma exacerbations, because subsequent admission need is directly related to time to receipt of systemic steroids, yet delays to administration remain long.

WHAT THIS STUDY ADDS: A medical directive allowing nurse initiation of oral corticosteroids before physician assessment was associated with improved quality and efficiency of care provided in the pediatric emergency department by ensuring implementation of evidence-based practice.

<table>
<thead>
<tr>
<th>TABLE 3 Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Hospital admission rate</td>
</tr>
<tr>
<td>Time to receipt of steroids</td>
</tr>
<tr>
<td>Time to “mild” status</td>
</tr>
<tr>
<td>Time to discharge</td>
</tr>
</tbody>
</table>

IQR, interquartile range; OR, odds ratio.

*Adjusted for preceding URTI and use of salbutamol, oral montelukast, chronic inhaled corticosteroids, and for previous ICU admission using logistic regression. Time to events was compared between phases by using Cox proportional hazards regression.
Dexamethasone vs. prednisone for asthma meta-analysis

Keeney et al. Pediatrics 2014;133:493-9

Relapse to ED
RR 1.07, 95% CI 0.77–1.50

Vomiting in ED
RR 0.29, 95% CI 0.12–0.69

Keeney et al. Pediatrics 2014;133:493-9
Ipratropium: Cochrane meta-analysis

Reisman 1988
Schuh 1995
Peterson 1996
Qureshi 1998
Zorc 1999

Total
Severe only

RR = 0.75 (0.62 - 0.89)
NNT = 12 (8 - 32)

RR = 0.74 (0.59 – 0.93)
NNT = 7 (5 – 20)

Relative risk for hospitalization

Plotnick et al. Cochrane database, 2003
Magnesium
Ciarallo et al, 1996

- Eligibility:
  - 31 children age 6-18 yrs
  - PEFR < 60% predicted after 3 doses albuterol

- Intervention:
  - All received corticosteroids
  - Randomized to MgSO₄ (25/kg, max. 2g) IV vs. NS

- Outcomes:
  - FEV1, peak flow
  - ED disposition
Magnesium
Effect on pulmonary function: Ciarallo et al., 1996

FEV1 (% of predicted)

Discharged
Mg 4/15
Placebo 0/16

* p< 0.05
Higher dose magnesium: Ciarallo et al., 2000

![Graph showing FEV % Improvement over time for different doses of magnesium.](image-url)

- 25/kg
- 40/kg

* Indicates a statistically significant difference.
Magnesium Summary

• Mentioned in NHLBI Guidelines as a rescue medication
• Should we be using IV Mg more regularly?
  – Survey: Concerns about adverse effects, monitoring, IV
    Schuh et al. Acad Emerg Med 2010
  – PECARN Registry: Low use, no increased revisits after discharge
    Johnson et al. PAS Meeting 2017
• Nebulized Mg:
  – MAGNETIC study - Powell et al. Health Tech Assess 2013
    • Multicenter study of 508 children in the United Kingdom
    • Randomized to Mg/NS given with albuterol / ipratropium x 3
    • 1 hour score: Clinically insignificant improvement in Mg group
  – Ongoing Canadian study (MagNUM PA): Nebulized Mg as rescue
Top 5 Reasons to Become an EM Researcher

2. Collaborate in research networks

3. Travel and meet colleagues around the world

4. Build a career in academic medicine

5. New opportunities to translate evidence effectively
Corticosteroids

- Multicenter randomized trial of infants with bronchiolitis
- 600 infants < 12 months with 1st episode wheeze
- RDAI score > 6 (maximum of 17)
- Randomized to one dose oral dexamethasone vs. placebo
- Respiratory treatments per MD discretion: 80% albuterol / 15% epi

Results
- No difference in hospitalization or severity score between groups

Corneli et al. NEJM 2009
Subgroup Analysis

Risk of Hospitalization

- Overall
- Atopy
  - History of eczema or family history of asthma
  - No history of eczema or family history of asthma
- RSV
  - Positive
  - Negative
  - Not tested
- Age
  - ≤6 mo
  - >6 mo
Multicenter randomized trial of infants with bronchiolitis

800 infants < 12 months with 1st episode wheeze

RDAI score ≥ 4 (maximum of 17)

Randomized to 4 groups:
- Nebulized Saline / Oral Placebo
- Nebulized Epinephrine / Oral Placebo
- Nebulized Saline / Oral Dexamethasone
- Nebulized Epinephrine / Oral Dexamethasone

Admission by day

Hospitalization by day 7

- 26.4% Placebo
- 25.6% Dex NS
- 23.7% Epinephrine NS
- 17.1% Epi + Dex

p = 0.07

NNT = 11
RR = 0.64

Subgroups?
Practice Variation in Acute Bronchiolitis: A Pediatric Emergency Research Networks (PERN) Study
Suzanne Schuh and TNTC others

Variation Across Global Networks

Pharmacotherapy

Chest Radiography
Prospectively studied 265 infants 2-23 mos. w/ bronchiolitis

- Defined “typical bronchiolitis”
  - Non-toxic appearance, cold symptoms, cough, 1st wheeze
  - Excluded children with chronic disease, prematurity, OM

- All received chest radiographs, reviewed by 2 radiologists
- Asked ED MD about antibiotic treatment pre/post X-ray

- Results:
  - Routine CXR no benefit (2 incidental findings, ? 1 “lobar”)
  - 1 extra antibiotic course for every 9 CXRs
Mild hypoxemia in the ED: Schuh et al. JAMA 2014

RCT of previously healthy infants at Toronto Sick Kids
- 4 weeks – 12 months old
- Mild-moderate bronchiolitis
- Oxygen sat ≥ 88%
- Randomized after triage
- Intervention: pulse ox ↑ 3%

Outcomes
- Admission rate: 41% vs 25%
  ARR 16%, RR=0.6, p=0.005
- Revisits: 21% vs 14%
Hypoxemia after ED discharge

- Prospective cohort: 118 infants after ED d/c for bronchiolitis
- Oxygen saturation measured with blinded pulse oximeter
- Measured desaturations at home lasting > 1 minute:
  - 64% had > 1 desaturation < 90%
  - 50% had > 1 desaturation < 80%
  - 24% had > 1 desaturation < 70%
  - Median desaturation lasted 3 minutes 22 seconds
- Infants with desaturation had similar outcomes to those w/o:
  - Unscheduled medical visits: 24% vs 26%
  - Hospitalization: 1% vs 5%

*Principi et al. JAMA Pediatr 2016*
High-flow nasal cannula oxygen

- Australian single center RCT:
  - 202 children 0-24 mos. with moderate bronchiolitis
  - Reduced treatment failure with HFNC: 33% vs 14%
  - 61% of failures on standard O₂ rescued with HFNC
  - No difference in ICU transfer rates: 12% vs 14%
  - No difference in hospital LOS

Kepreotes et al. Lancet 2017
HFNC Multi-center

PREDICT Network multi-center RCT:
- 1,472 children < 12 months with bronchiolitis requiring O$_2$
- HFNC 2 L/kg/min vs. standard 0-2 L/min oxygen
- Reduced escalation with HFNC: 23% vs. 12%, NNT 9
- 61% of failures on standard O$_2$ rescued with HFNC
- No difference in ICU transfer rates: 9% vs 12%
- No difference in hospital LOS

Franklin et al. NEJM 2018
Top 5 Reasons to Become an EM Researcher

1. Impact patients and improve care
2. Collaborate in research networks
3. Travel and meet colleagues around the world
4. Build a career in academic medicine
5. New opportunities to translate evidence effectively
## Bronchiolitis

### Initial Management
- Suctioning
- Repeat assessments
- Routine care:
  - No CXR or viral test
  - No bronchodilators

### Severe Disease
- HFNC Oxygen
- Epinephrine

## Asthma

### Early steroids

### Severity assessment
- Mild-moderate: MDI
- Severe:
  - Continuous albuterol
  - Ipratropium

### IV Magnesium