Top Ten Pediatric Infectious Disease Articles of 2014

Michael Radetsky MD CM
Albuquerque NM
Financial Disclosure

• No relevant financial relationships with any commercial interests.
Top Ten Pediatric Infectious Disease Articles

Selection criteria

• The theme is common in the daily practice of pediatrics
• The results make a difference
• The article is IMMEDIATELY useful
Top Ten Objectives-1

Learn more about:

- Sitting vs flexed position in infant LP
- Accuracy of pulse oximetry in children
- Diagnosis in lethargic or poorly feeding infants
- Clinical pathway for suspected appendicitis
- New approach to decided which newborns require sepsis evaluation
Top Ten Objectives-2
Learn more about:

• Treatment of bronchiolitis with hypertonic saline nebulizers
• Routine screening for viruses is acute respiratory infection
• Should oseltamivir be used to treat real or suspected influenza infection
• Probiotics in infant colic
• Use of the urine dipstick in management of febrile infants
Article 10
Analysis of infant lumbar puncture success rates
Sitting flexed versus lateral flexed positions

• Lanson AL, Ros S, Sporano J
• Loyola University Medical Center, IL
• Pediatr Emerg Care 2014;30:311-314
Lumbar puncture-1
Background

- **Pediatr Emerg Care 2004;20:816-820**
  - 82% academic ED MD’s prefer lateral flexed position.
  - 39% academic ED MD’s would change position based on holder preferences.

- **J Pediatr 2011;158:33-37**
  - Opening pressures rarely performed in children; hence sitting flexed position is a viable option.
Methods

• Retrospective chart review.
• Age: 0-365 days.
• LP performed for any indication in ED.
• Data Gathered
  – Position during LP
  – Number of LP attempts
  – Success rates
  – Amount sufficient for culture & cell count
  – CSF RBC : <500 or <10,000.
Lumbar puncture-3

Results

• 132 patients had complete data.
• Sitting flexed = 30; lateral flexed = 102.
Lumbar puncture-4
Conclusions

• Quantity of fluid and risk of traumatic tap was the same in both groups.
• CSF was more likely to be obtained on the first attempt if the patient was in the sitting flexed position.
• Ultrasound study showed the interspinous space is maximized in the sitting flexed position (Pediatrics 2010;125:e1149-e1153).
• Sitting flexed position has smallest changes in O2 saturations in preterms (Pediatrics 1983;71:31-35).
Article 9
Accuracy of pulse oximetry in children

- Ross PA, Newth CJL, Khemani RG
- Children’s Hospital Los Angeles
- *Pediatrics* 2014;133:22-29
Accuracy of pulse oximetry-1
Methods-1

• Prospective, observational study.
• 5 US multidisciplinary PICUs
• Inclusion
  – Intubated and ventilated
  – Had arterial catheter
  – Had SpO2 values between 65% and 97%.
• Exclusion
  – ECMO
Accuracy of pulse oximetry-2
Methods-2

- SpO2 documented at time of ABG.
- SaO2 measured via co-oximetry.
- Goal: evaluate accuracy of SpO2 compared to SaO2.
- $A_{\text{arms}} = \text{accuracy root mean squared; FDA threshold} < 3\%.$

$$A_{\text{rms}} = \sqrt{\frac{\sum_{i=1}^{N}(SpO_{2i} - SaO_{2i})^2}{n}}$$
Accuracy of pulse oximetry-3

Results-1

• 225 children enrolled; 1980 SaO₂/SpO₂ pairs obtained.
Accuracy of pulse oximetry

Results

Accuracy ($A_{\text{rms}}$) vs. $\text{SpO}_2$ (%)
Accuracy of pulse oximetry-5

Conclusions

• Pulse oximeters overestimate oxygen saturations by ~5%.
• Such bias is most marked at saturations between 81% and 85% and least apparent at saturations > 95%
• Increased bias in patients with poor capillary refill in extremity with probe.
• Caution must be exercised in making clinical choices when a SpO2 of 5% lower would make a difference.
Use of pulse oximetry to exclude pneumonia in children

• Tanen DA, Trocinski DR
• Naval Medical Center, San Diego
Pulse oximeter and pneumonia-2

• **Methods**
  – Retrospective chart review over 1 year
  – Children < 24 months with respiratory complaints presenting to ED
  – Pulse oximetry and chest x-ray performed

• **Results**
  – 807 met inclusion criteria
  – 78 cases of radiologic pneumonia
Pulse oximeter and pneumonia

Logistic regression:
Pulse oximeter saturations could not predict lung opacity
Office Use of Pulse Oximetry: Conclusions

• **Presence of pneumonia**: no better than clinical impression (WHO criteria) in predicting the presence of radiologic pneumonia but may help in decision to hospitalize

• **Best use**: “tie breaker” when clinical judgment is equivocal, especially in infants
Impact of pulse oximetry and oxygen therapy on length of stay in bronchiolitis hospitalizations

• Schroeder AR, Marmor AK, Pantell RH, Newman TB.

• *Arch Pediatr Adolesc Med* 2004; 158:527-530

• University of California, San Francisco
Pulse oximetry in bronchiolitis-2

Methods

• Retrospective medical chart review
• Bronchiolitis < 2 years-old hospitalized
• “Widely accepted discharge criteria”
  – Feeding well, minimal respiratory distress, no social issues, nebs < q 4 hours
• Calculated number of days hospitalization prolonged solely due to “low” pulse oximeter saturation as documented in physician notes
Pulse oximetry in bronchiolitis-3

Results

- 62 patients
- Pulse ox used in 100% of patients
- Range of target O2 cutoffs (figure)
- 26% prolonged stay due to “low” SpO2
- Average prolonged stay: 1.6 days
Pulse oximetry in bronchiolitis-4

Conclusions

- Pulse oximetry is universally used for hospitalized infants with bronchiolitis
- Minimum saturation cutoffs are arbitrary and vary widely among physicians
- Many infants, otherwise ready for home discharge, become “prisoners” of the pulse oximeter, with inappropriately prolonged hospital stays
Saturations in healthy infants during first 6 months of life

- Collaborative Home Infant Monitoring Evaluation study (CHIME) - 7 low-elevation sites
- Infants followed prospectively from 2-25 weeks of age
- 64 infants
- 35,127 3-minute epochs recorded
SpO2 in healthy infants-2
Median baseline SpO2
59% infants had ≥1 desaturation events (average 4; range 1-71); median lowest SpO2 83% (10th%, 90th% = 78%, 87%); highest frequency during supine sleep
SpO2 in healthy infants-4

Conclusions

• At sea level, persistent SpO2 < 95% is abnormal

• Occasional desaturation is normal during first 6 months of life

• Level of baseline saturation or number, duration, depth of desaturations which require intervention is unknown

• Poets, CF. J Pediatr 1999;135:541
Office Use of Pulse Oximetry: Conclusions

• **Severity of disease:** no better than clinical impression (WHO criteria) in predicting the presence of radiologic pneumonia but may help in decision to hospitalize.

• **Predict clinical course:** useful to predict likely course of acute asthma.

• **Determine oxygen need:** Generally accurate, but beware the arbitrary threshold.

• **Best use:** as a “tie breaker” when clinical judgment is equivocal, especially in infants.
When do sick infants need additional inspired oxygen?

• No one knows
• Rates of SIDS reduced and weight gain enhanced in infants with chronic lung disease if SpO2 > 93%
• O2 given to mildly hypoxemic infants (SpO2 89%) decreased airway and pulmonary artery resistances by 50%
• Poets CF. *Pediatr Pulmonol* 1998;26:424-428
Article 8
Diagnostic findings in infants presenting to a pediatric emergency department for lethargy or feeding complaints

- Webb T, Nugent M, Simpson P, Melzer-Lange M
- Medical College of Wisconsin, Milwaukee
- *Pediatr Emerg Care* 2014;30:151-156
Findings in lethargic infants-1
Methods-1

• Retrospective chart review 2005-2009.

• Inclusion
  – Age ≤ 6 months.
  – “Lethargy” or “poor feeding” listed in Chief Complaint in ED Triage record.

• Exclusion
  – T ≥ 38°C; T ≤ 36°C.
  – Trauma, chronic disease
  – Prematurity < 35 wk GA
Findings in lethargic infants-2
Methods-2

• Data elements
  – Age, gender, ethnicity, triage level, duration of symptoms, presence/absence of feeding issue; type of feeding; vital signs; perfusion status; “ill vs well” appearance, diagnostic testing, IV fluids, antibiotics, physician level of training, disposition, final ED diagnosis.
Findings in lethargic infants-3
Results-1

• During 6 year study period, 35,931 patients ≤ 6months presented to ED.
• 352 (1%) had Chief Complaint contain “lethargy” or “poor feeding.”
• 272/352 (77%) included in study: 102 feeding complains alone, 30 lethargy alone, 140 both.
• 261/272 (96%) were “well-appearing/non-toxic” vs 11/272 (4%) “ill/toxic.”
Findings in lethargic infants-4
Results-5

Numbers of Infants

Diagnostic Test Performed

- CBC
- BCx
- UA
- UC
- CSF cell count
- CSF culture
- BMP
- Bilirubin
- AXR
- Head CT

Abnormal
Normal
Findings in lethargic infants-5
Results-3

• Management
  – 15% received antibiotics; 11% had IV fluid bolus; 79% were sent home; 19% were admitted to the hospital pediatric ward (dehydration, hyperbilirubinemia; 2% were admitted to the PICU.
  – Of the 215 infants sent home, 3% had a return visit to ED within 1 week; none had a condition leading to intervention or monitoring.
Findings in lethargic infants-6
Results-4

• 34/272 (12.5%) had diagnoses leading intervention or monitoring:
  – 17 hyperbilirubinemia
  – 8 dehydration
  – 2 intracranial bleeds
  – 3 SBI (all UTI; all “ill/toxic”)  
  – 1 cardiac disorder (SVT)
  – 2 neurological disorder (1 congenital hypotonia, 1 fiber-type dysplasia)
  – 1 thrombocytopenia
Findings in lethargic infants-7
Results-5

Well-appearing (n=261)
- Diagnoses with no intervention (n=235)
  - Focal findings on clinical evaluation (n=26)

- Diagnoses requiring intervention (n=26)

Ill-appearing (n=11)
- Focal findings on clinical evaluation (n=4)
- No focal findings (n=7)
  - Thrombocytopenia (n=1)
  - No etiology determined (n=3)
  - SBI (n=3)
Findings in lethargic infants-8
Conclusions-1

• In young infants with the Chief Complaints of “lethargy” or “poor feeding,” 87.5% had no condition which required intervention.

• Of the 12.5% of infants who ultimately required intervention, all were identified on the clinical evaluation: either focal findings (e.g. jaundice, dehydration, tachycardia, CNS abnormalities) or by “ill/toxic” appearance.
Findings in lethargic infants-9
Proposed management scheme

Well-appearing

Physician evaluation reassuring

No further testing indicated (0 percent req intervention)

Ill-appearing

Physician evaluation suggestive of dehydration, jaundice or other focal disorder

Targeted evaluation based on physician evaluation; consider sepsis evaluation

Focal findings on clinical evaluation

Evaluation for sepsis (67% req intervention)

No focal findings
Article 7
Prospective evaluation of a clinical pathway for suspected appendicitis

- Saucier A, Huang EY, Emeremni CA, Pershad D
- Le, Bonheur Children’s Hospital, Memphis
- *Pediatrics* 2014;133:e88-e95
Suspected appendicitis-1
Methods-1

• Prospective, observational study at urban pediatric ED.

• Inclusion: Convenience sample of 3-18 years-old patients with abdominal pain and suspicion of appendicitis.

• Exclusion: IBD; SSD; chronic steroids, immunosuppression, prior CT by referring hospital, or taking antibiotics.

• All patients: NS bolus, CBC, UA, CBP.
Suspected appendicitis

Methods

• Pediatric appendicitis score (PAS) assigned
• Risk stratification:
  – 1-3 = negative
  – 4-7 = ??
  – 8-10 = positive

• *J Pediatr Surg*
  2002;37:877-881

<table>
<thead>
<tr>
<th>Signs/Symptoms</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough/heel whack ➔ RLQ tenderness</td>
<td>2</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
</tr>
<tr>
<td>T≥38°C</td>
<td>1</td>
</tr>
<tr>
<td>Nausea/emesis</td>
<td>1</td>
</tr>
<tr>
<td>RLQ pain on light palpation</td>
<td>2</td>
</tr>
<tr>
<td>WBC &gt; 10,000</td>
<td>1</td>
</tr>
<tr>
<td>%Segs&gt;75%</td>
<td>1</td>
</tr>
<tr>
<td>Pain migration to RLQ</td>
<td>1</td>
</tr>
</tbody>
</table>
Suspected Appendicitis 4–17 y

CBC, BMP, UA, IVF, ± CXR, KUB,

PAS 1–3
- Discharge with follow-up phone call
- "Negative" for appendicitis
  - Consult Pediatric Surgery if continued suspicion or discharge with follow-up phone call

PAS 4–7
- USG
  - "Positive" for appendicitis
    - Consult Pediatric Surgery

PAS 8–10
- Consult Pediatric Surgery
Suspected appendicitis-3
Results-1

• PAS stratification of 196 study patients:
  – 1-3 = 22.4%; 4-7 – 60.7%; 8-10 – 16.9%.

• PAS in appendicitis = 65 patients
  – 1-3 – 0%; 4-7 – 57%; 8-10 – 43%.

• Appendicitis in PAS
  – 1-3 – 0%; 4-7 – 31%; 8-10 – 85%.

• Ultrasound performed in 65% of cases
  – 37.5% were positive for appendicitis

• CT scan performed in 6%.
Suspected appendicitis-4
Results-2

• Surgery performed in 68/196 (35%); 3/68 (4%) had a normal appendix.
• 97/196 (49.5%) children were sent home.
• One child sent home with intermediate PAS and negative ultrasound was readmitted the next day with a ruptured appendix.
## Suspected appendicitis-5
### Results-3

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Appendicitis (+)</th>
<th>Appendicitis (-)</th>
<th>PPV = 90%</th>
<th>NPV = 96%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathway (+)</td>
<td>60</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathway (-)</td>
<td>5</td>
<td>124</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prevalence = 33%

Sens = 92%

Spec = 95%

N=196
Suspected appendicitis-6

Conclusions

• Risk stratification using PAS supplemented by US was a highly successful management tool.
• The need for CT scan was kept to a minimum.
• Clinical judgment plus a field-tested clinical pathway offers an accurate approach to suspected childhood appendicitis.
Article 6
Stratification of risk of early-onset sepsis in newborns ≥ 34 weeks’ gestation

• Escobar GJ, Puopolo KM, Wi S, et al
• Kaiser Permanente of Northern California
• Pediatrics 2014;133:30-36.
Risk of early onset sepsis-1
Methods-1

- Retrospective case controlled study.
- Base population: 608,014 live births 1993-2007 at 12 California K-P hospitals + Brigham and Women’s Hospital and Beth Israel-Deaconess Medical Center, Boston.
- All newborns ≥ 34 weeks gestation with culture-confirmed bacterial sepsis < 72 hr. of life.
- 350 cases matched with 1063 controls.
Methods


- In a derivation set of 167 cases + 494 controls, recursive partitioning, logistic regression, and consultation with neonatologists resulted in risk stratification scheme using clinical signs.

- Tested on verification set of patients.
Risk of early onset sepsis-3
Classification of clinical signs-1

• “Clinical illness” (either):
  – 1\textsuperscript{st} 12 hrs: Any: 5 min Apgar <5, nasal CPAP or ventilation, vasoactive drug infusion, seizure
  – 1\textsuperscript{st} 6 hrs: Significant respiratory distress with O2 need ≤ 6 hrs.
Risk of early onset sepsis-4
Classification of clinical signs-2

• “Equivocal presentation” (1st 12 hrs:” at least 2 instances of 1 or more):
  – [“Instance” = ≥ 2 measurements ≥2 hrs apart]
  – HR ≥160.
  – RR ≥60.
  – T ≥100.4°F or <97.5°F.
  – Respiratory distress without O2.
Risk of early onset sepsis-5
Classification of clinical signs-3

• “Well appearing”
  – 1st 12 hrs: Infant did not fall into other two groups.
Risk of early onset sepsis-6

Results-1

• Likelihood ratios for early onset sepsis for three clinical categories:
  – Clinical illness = 14.5.
  – Equivocal presentation = 3.75.
  – Well appearing = 0.36

• Calculator for estimating the probability of early onset sepsis based on maternal risk factors *Pediatrics 2011;128:e1155*

• [https://extapps.kaiser.org/escobar/nis3sepsisriskatbirth.xls](https://extapps.kaiser.org/escobar/nis3sepsisriskatbirth.xls)
Probability of Neonatal Early-Onset Infection Based on Maternal Risk Factors

The tool below is meant for clinicians who are interested in calculating the risk of early-onset infection among infants born at or above 34 weeks gestation.

The interactive calculator produces the probability of early-onset infection per 1000 babies by entering values for each maternal risk factor. This calculator is based on the predictive model described in Karen M. Puopolo, MD, PhD, David Draper, PhD, Soora Wi, MPH, Thomas B. Newman, MD, MPH, John Zupancic, ScD, MD, Elice Lieberman, DrPH, MD, Myesha Smith, BS, and Gabriel J. Escobar, MD, "Estimating the Probability of Neonatal Early-Onset Infection on the Basis of Maternal Risk Factors" in the journal Pediatrics 2011;128:e1155-e1163.

<table>
<thead>
<tr>
<th>Maternal Predictor</th>
<th>Scenario</th>
<th>Example Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td>weeks days</td>
<td>35 weeks 5 days</td>
</tr>
<tr>
<td>Highest maternal antepartum temperature</td>
<td>Fahrenheit</td>
<td>99.5°F</td>
</tr>
<tr>
<td>ROM (hours)</td>
<td></td>
<td>12.7</td>
</tr>
<tr>
<td>Maternal GBS status</td>
<td>Negative Positive Unknown</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Type and timing of intrapartum antibiotics
Select only 1 category. If both Broad spectrum and GBS-specific intrapartum antibiotics were given, please select the appropriate timing among the Broad spectrum categories.

- Broad spectrum ≥ 4 hrs prior to birth
- Broad spectrum < 4 hrs prior to birth
- GBS-specific at anytime
- None

Predicted probability per 1000 babies

[Calculate]  [Clear]

Detailed Interpretation

(Show)
## TABLE 3 Updated Posterior Probability and NNTa

<table>
<thead>
<tr>
<th>Clinical Presentationb</th>
<th>Previous Probability (Sepsis Risk at Birth, Based on Maternal Risk Factorsb) Rate per 1000 Live Births</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.65</td>
</tr>
<tr>
<td>Well appearing</td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>0.11 (0.08–0.13)</td>
</tr>
<tr>
<td>NNT</td>
<td>9370 (7418–12 073)</td>
</tr>
<tr>
<td>Equivocal presentation</td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>1.31 (0.93–1.84)</td>
</tr>
<tr>
<td>NNT</td>
<td>763 (543–1076)</td>
</tr>
<tr>
<td>Clinical illness</td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>4.66 (2.80–8.04)</td>
</tr>
<tr>
<td>NNT</td>
<td>214 (124–357)</td>
</tr>
</tbody>
</table>

a Odds ratio compared to healthy newborns
b For unstable presentation, 49.5% of infants born to women with risk factors, 41.6% of infants born to untreated mothers, and 16.2% of infants born to untreated mothers

Risk of early onset sepsis-8
Conclusions-1

- A quantitative risk-stratification strategy for early-onset sepsis is available.
- This calculation of risk, along with the number-needed-to-treat (NNT) may be used to augment clinical judgment in the management of infants ≥34 weeks gestational age.
## Risk of Early Onset Sepsis

### Conclusions

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Sepsis Risk at Birth Estimated from Maternal Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 0.65/1000 live births</td>
</tr>
<tr>
<td>Well appearing</td>
<td><strong>Continued Observation</strong></td>
</tr>
<tr>
<td></td>
<td>85% of live births</td>
</tr>
<tr>
<td></td>
<td>NNT=9,370</td>
</tr>
<tr>
<td>Equivocal presentation</td>
<td><strong>Observe and Evaluate</strong></td>
</tr>
<tr>
<td></td>
<td>11% of live births</td>
</tr>
<tr>
<td></td>
<td>NNT=823</td>
</tr>
<tr>
<td>Clinical illness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Article 5
Nebulized hypertonic saline for bronchiolitis. A randomized clinical trial

- Wu S, Baker C, Lang ME et al.
- Children’s Hospital Los Angeles
Hypertonic saline for bronchiolitis-2

Methods-2

- Randomized: 3% hypertonic saline (HS) vs 0.9% normal saline (NS).
- 2.5 mg of nebulized albuterol + 4 ml of saline, maximum 3 doses every 20 min.
- Admitted patients received 4 ml saline q 8 hr. until discharged
- Outcomes: Admission rate, LOS, Respiratory Distress Assessment Instrument (RDAI) and change.
<table>
<thead>
<tr>
<th>Wheezing</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Max points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expiratory</td>
<td>None</td>
<td>End</td>
<td>½ exp</td>
<td>≥ ½ exp</td>
<td>All</td>
<td>4</td>
</tr>
<tr>
<td>Inspiratory</td>
<td>None</td>
<td>Part</td>
<td>All</td>
<td>N/A</td>
<td>N/A</td>
<td>2</td>
</tr>
<tr>
<td>Location</td>
<td>None</td>
<td>Segmental</td>
<td>Diffuse</td>
<td>N/A</td>
<td>N/A</td>
<td>2</td>
</tr>
<tr>
<td>Retractions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superclavicular</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Marked</td>
<td>N/A</td>
<td>3</td>
</tr>
<tr>
<td>Intercostal</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Marked</td>
<td>N/A</td>
<td>3</td>
</tr>
<tr>
<td>Subcostal</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Marked</td>
<td>N/A</td>
<td>3</td>
</tr>
</tbody>
</table>
Hypertonic saline for bronchiolitis-3

Results

• 408 infants enrolled and randomized.
• Admission rate: NS = 42.6%; HS = 28.9%; OR = 0.45; p = 0.1.
• LOS: NS = 3.92 days; HS = 3.16 days; p = 0.24.
• RDAI: no difference NS vs HS in change from pre- to post-treatment.
• Supplemental therapies: no differences
Hypertonic saline for bronchiolitis-4

Conclusions

• HS significantly reduced the hospital admission rate when given in ED.
• NNT to prevent 1 hospitalization was 8 patients.
• There were no other study differences between NS and HS.
Nebulized hypertonic saline for bronchiolitis in the ED: A randomized clinical trial

- Florin TA, Shaw KN, Kittick M, et al.
- Children’s Hospital of Philadelphia
Hypertonic saline for bronchiolitis in ED-1

Methods

• Double-blind, randomized clinical trial ED at a single tertiary urban children’s hospital.

• Inclusion
  – Age: 2-24 months.
  – Primary diagnosis = bronchiolitis.
  – 2 consecutive bronchiolitis seasons.

• Exclusion
  – History of prior wheezing, chronic lung or heart disease, critical illness
Hypertonic saline for bronchiolitis in ED-2

Methods-2

• 2.5 mg albuterol neb + 4 ml NS or HS.
• Additional doses per MD.

• Outcome:
  – Change in RDAI at 1 hour after therapy.
  – Vital signs.
  – O2 sats.
  – Admission rate.
Hypertonic saline for bronchiolitis in ED-3

Results

- 62 infants enrolled.
- NS group displayed improvement 1 hour after therapy vs no improvement in HS group.
- At 2 hours after therapy, there were no differences in clinical illness between groups.
- No other differences between the groups in any other outcome measurement.
Hypertonic saline for bronchiolitis in ED-4

Conclusions

• Infants given NS vs HS had greater improvement in clinical illness at 1 hour after treatment.

• There were no other differences between the two groups.
A tale of 2 trials: Disentangling contradictory evidence on hypertonic saline

- Grewal S, Klassen TP
- Departments of Pediatrics, University of Alberta and University of Manitoba
A tale of 2 trials-1

• Studies by Florin and Wu appeared to reach different conclusions.
• Both were randomized, controlled trials (RCT). Both were well designed and implemented. Patient populations were equivalent.
• Neither study had large numbers.
• Consequently, the best source of guidance would be a well-designed meta-analysis.
A tale of 2 trials-2

• Such a systematic review was published in 2013 in the Cochrane Database
  – 11 trials involving 1090 infants. All but one of the trials were of high quality with low risk of bias.
  – HS could lead to a reduction of 1.2 days in mean LOS and improve clinical severity scores over days but not within hours.

• The studies by Florin and Wu need to be incorporated into an updated review.
Article 4
Clinical utility of PCR for common viruses in acute respiratory illness

- Karolinska Institute, Stockholm
- Pediatrics 2014;133:e538-e545
PCR for common viruses-1

Methods-1

• Matched case-control study.
• ED at Sachs’ Children’s Hospital
• Inclusions
  – Age ≤ 5 years.
  – ≥1: coryza, sore throat, earache, cough, sputum production, dyspnea.
• One control for each study patient.
• Clinical parameters recorded.
PCR for common viruses-2
Methods-2

• NP aspirates from study and control patients submitted for PCR, 16 viruses:
  – Influenza A seasonal, influenza A H1Nipdm09, influenza B, adenovirus, bocavirus, coronavirus, enterovirus, metapneumovirus, rhinovirus parainfluenza 1-3, RSV.
PCR for common viruses-3
Results-1

- 209 each of study patients and control subjects were enrolled.
- Respiratory viruses were detected in 72% of study patients
- Virus was found in 35% of control subjects, but rarely RSV, hMPV, or PIV.
- In 42/209 (20%) study patients, >1 virus was detected.
PCR for common viruses-4
Virus isolation in clinical illness

![Bar chart showing percentage of patients with different viruses and conditions](chart.png)
PCR for common viruses-5
Virus detection in (A) study patients and (B) control subjects
Conclusions

• Virus was found in 72% of symptomatic children and 35% of asymptomatic control subjects.
• PCR finding of RSV, hMPV, and PIV is likely to be causative in children with acute respiratory infection; finding of other viruses must be interpreted with caution.
• Multiple viruses were found in 20% of study patients, but it’s clinical significance is not known.
Rapid viral diagnosis for acute febrile respiratory illness in children in the Emergency Department

- Systematic review.
- The Cochrane Collaboration
Rapid viral diagnosis in ED

Results

- 3 randomized controlled trial and one quiz-RCT were included, with 759 in the rapid viral testing group and 829 in the control group.
- Rapid viral testing did not reduce antibiotic use the ED, result in shorter length of stay, or decrease ordering of blood or urine tests. Chest x-rays were ordered less frequently (RR = 0.77)
- Current evidence is insufficient to support routine rapid viral testing.
Article 3
Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments

• Jefferson T, Jones M, Doshi P, et al.
• University of Queensland, Brisbane, University of Maryland, Oxford Univ.
• BMJ 2014;348:g2545 doi: 10.1136.bmj.g2545
Oseltamivir for influenza-1

Methods-1

• Variety of methods applied to different sources (publications, registries, correspondence with manufacturers, review of regulatory documents).


• Meta-analysis performed of qualifying studies.
Oseltamivir for influenza-2

Methods-2

• Included: Randomized, controlled trials testing effects of oseltamivir for treatment, prophylaxis, and post-exposure prophylaxis of influenza.

• Trials of both children and adults.

• Extensive use of published criteria for assessing validity of study data (Cochrane Database of Systematic Reviews 2011;1:CD008965. doi: 10.1002/14651858)
Oseltamivir for influenza-3
Results-1

• 83 eligible trials identified.
• 63 were excluded for flaws in study design, bias, data reporting.
• 11/20 adequately reported random sequence generation; 15/20 showed adequate allocation concealment; 11/20 showed adequate blinding of participants and staff; 19/20 showed adequate blinding of outcome assessors; 20/20 were under-recruited.
Oseltamivir for influenza-4

Results-2

• Adults
  – Oseltamivir reduced time to first alleviation of symptoms by 16.7 hours.
Oseltamivir for influenza-5
Results-3

- **Children**
  - 1 trial in healthy children favored oseltamivir, but 3 trials in asthmatic children showed no benefit.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Oseltamivir</th>
<th>Placebo</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.46.1 Otherwise healthy children</td>
<td>331 159.6</td>
<td>338 37.2</td>
<td>-29.40 [-47.04, -11.76]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>331</td>
<td>338</td>
<td>-29.40 [-47.04, -11.76]</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.27 (P = 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Oseltamivir</th>
<th>Placebo</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NV16871 88.6 98 165 82.5 75.7 164 36.2</td>
<td>333</td>
<td>327</td>
<td>5.18 [-11.06, 21.41]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>333</td>
<td>327</td>
<td>5.18 [-11.06, 21.41]</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.85); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.63 (P = 0.53)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total (95% CI)</th>
<th>664</th>
<th>665 100.0</th>
<th>-8.04 [-33.34, 17.26]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterogeneity: Tau² = 366.79; Chi² = 8.03, df = 2 (P = 0.02); I² = 75%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.62 (P = 0.53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 7.99, df = 1 (P = 0.005), I² = 67.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Favours oseltamivir
- Favours placebo
Oseltamivir for influenza-6

Results-4

- Adults and children
  - No difference in rates of admission to hospital between treatment groups
Oseltamivir for influenza-7

Results-5

• Adults and children
  – No differences in risks of mild complications (sinusitis, otitis media) or severe complications (leading to withdrawal from study)
Oseltamivir for influenza-8
Results-6

• Adults
  – Oseltamivir reduced unverified, self-reported pneumonia risk (RR = 0.55), but NNT = 100.

• Children
  – No significant difference in influenza related pneumonia risk.
Oseltamivir for influenza-9
Results-7

• Adults and children
  – In prophylaxis trials, oseltamivir reduced symptomatic influenza in participants by 55%, NNT = 33 and in households by 80%, NNT = 8.

• Adults and children
  – Deaths due to influenza were no different between treatment groups.
Oseltamivir for influenza-10

Conclusions

– In adults, oseltamivir’s effect on the clinical course of symptomatic influenza is modest.
– In children, there is no significant effect of oseltamivir on clinical influenza infection.
– As prophylaxis, oseltamivir reduced the risk of symptomatic influenza (but no evidence that it prevents influenza-like illness).
– Oseltamivir did not prevent death.
– It is unproven whether oseltamivir can interrupt viral during pandemics.
CDC on oseltamivir meta-analysis – 4/10/14

“The Cochrane review did not consider any data from an abundance of observational studies of oral oseltamivir or inhaled zanamivir treatment. While such studies have inherent design limitations and potential biases, they can inform clinical practice and public health. Observational studies are especially important when data from RCTs are unavailable to address questions relevant to specific outcomes (like severe disease) or to certain high-risk groups, or because having a placebo group would be unethical since antiviral treatment is recommended for these groups. Observational studies have consistently found that early oseltamivir treatment of influenza patients reduces the duration of hospitalization and risk of severe outcomes.”
Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data

– University of Nottingham, UK
Neuraminidase inhibitors-2

Methods

• 78 treatment centers worldwide pooled hospital data on individual patients.
• Inclusion
  – Hospitalized patients with confirmed H1N1 influenza infection or influenza infection diagnosis made by clinical judgment during 2009-2011.
• Risk of mortality: NAI therapy vs no therapy; therapy < 2 days vs > 2 days.
Neuraminidase inhibitors-3
Results-1

<table>
<thead>
<tr>
<th>Group</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>0.7</td>
</tr>
<tr>
<td>Children &lt; 16</td>
<td>0.8</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>0.4</td>
</tr>
<tr>
<td>Critical care adults</td>
<td>0.7</td>
</tr>
<tr>
<td>Critical care children</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Statistically significant = p < 0.05**
Neuraminidase inhibitors - 4

Results - 2

**Figure 2: Survival by time to treatment**

HR = hazard ratio. NAI = neuraminidase inhibitor. *Cox regression shared frailty model (adjusted for treatment propensity and in hospital steroid or antibiotic use).
Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who
– is hospitalized;
– has severe, complicated, or progressive illness; or
– is at higher risk for influenza complications.
CDC Recommendations 2014-2

• Persons at higher risk for influenza complications recommended for antiviral treatment include:
  – children aged younger than 2 years;**
  – adults aged 65 years and older;
  – persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions, persons with immunosuppression, including that caused by medications or by HIV infection;
CDC Recommendations 2014-3

- Persons at higher risk for influenza complications recommended for antiviral treatment include:
  - women who are pregnant or postpartum (within 2 weeks after delivery);
  - persons aged younger than 19 years who are receiving long-term aspirin therapy;
  - American Indians/Alaska Natives;
  - persons who are morbidly obese (i.e., body-mass index is equal to or greater than 40); and
  - residents of nursing homes and other chronic-care facilities.
• “**Although all children aged younger than 5 years are considered at higher risk for complications from influenza, the highest risk is for those aged younger than 2 years, with the highest hospitalization and death rates among infants aged younger than 6 months. Because many children with mild febrile respiratory illness might have other viral infections, knowledge of other respiratory viruses as well as influenza virus strains circulating in the community is important for treatment decisions. The likelihood of influenza virus infection in a patient depends on the prevalence of influenza activity in the local community and on the patient’s signs and symptoms.”
Influenza mortality rates in 153 children 2003-2004


Deaths per 100,000 children in US

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 mo</td>
<td>0.88</td>
</tr>
<tr>
<td>6-11 mo</td>
<td>0.59</td>
</tr>
<tr>
<td>1 y</td>
<td>0.77</td>
</tr>
<tr>
<td>2 y</td>
<td>0.35</td>
</tr>
<tr>
<td>3 y</td>
<td>0.23</td>
</tr>
<tr>
<td>4 y</td>
<td>0.31</td>
</tr>
<tr>
<td>5-10 y</td>
<td>0.11</td>
</tr>
<tr>
<td>11-17 y</td>
<td>0.11</td>
</tr>
</tbody>
</table>
Influenza deaths in US children 2003-2004


Deaths by age in US

- <6 mo: 18
- 6-11 mo: 12
- 1 y: 31
- 2 y: 14
- 3 y: 9
- 4 y: 12
- 5-10 y: 26
- 11-17 y: 31

Total deaths = 153
The majority of PICU admissions and pediatric deaths from pH1N1 were in older children with high-risk medical conditions.
“As soon as a new but still unproved method of treatment is adopted by even a minority of the medical profession, it becomes virtually impossible to conduct the controlled trial that alone can furnish truly reliable evaluation of its effectiveness and its hazards”

Jennet B. Teasdale G. J Neurol Neurosurg Psychiatr 1980;43:289
Accuracy and interpretation of rapid influenza tests in children

• Grijalva CG, Poehling KA, Edwards KM, et al.
• Vanderbilt, Rochester, Cincinnati, CDC
• Pediatrics 2007;119 (1):e6-e11
Rapid influenza tests

Methods

• Multiple site study coordinated by the National Vaccine Surveillance Network
• Prospective enrollment 2000-2004
  – Hospitalized children < 5 year of age
  – Respiratory symptoms or fever
• Weekly prevalence rates derived from concurrent OPD surveys
Rapid influenza tests-2
Methods-2

• Viral cultures and RT-PCR testing performed on all hospitalized patients

• Rapid influenza testing ordered at discretion of attending MD

• Types of rapid influenza tests used
  – Directigen A+B
  – Quick Vue A/B
  – Directigen A
  – NOW Flu A/B
Rapid influenza tests-3
Results-1

• 2797 hospitalized children enrolled
• 160/2797 (6%) positive for influenza by culture or RT-PCR
• 270 children had rapid influenza tests
• 41/270 (15%) were culture/RT-PCR (+)
  – 26/41 (65%) rapid test (+) = sensitivity
• 229/270 (85%) were culture/RT-PCR (-)
  – 223/229 (97%) rapid test (-) = specificity
The four-square diagram

<table>
<thead>
<tr>
<th>(+) Disease</th>
<th>(-) Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+) Test</td>
<td>A</td>
</tr>
<tr>
<td>(-) Test</td>
<td>C</td>
</tr>
</tbody>
</table>

A + B = A+B
C + D = C+D
A + C = A+C
B + D = B+D

Sensitivity = \( \frac{A}{A+C} \)
Specificity = \( \frac{D}{B+D} \)
Positive Predictive Value (PPV) = \( \frac{A}{A+B} \)
Negative Predictive Value (NPV) = \( \frac{D}{C+D} \)
## Influenza Testing

### 2x2 Table

<table>
<thead>
<tr>
<th>Rapid Test</th>
<th>Influenza Present</th>
<th>Influenza Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>TP FP</td>
<td></td>
</tr>
<tr>
<td>(-)</td>
<td>15</td>
<td>223</td>
</tr>
<tr>
<td></td>
<td>FN TN</td>
<td>229</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>229</td>
</tr>
</tbody>
</table>

TP: True Positive  
FP: False Positive  
FN: False Negative  
TN: True Negative
Rapid influenza tests-4
Results-2

• Predictive value of rapid testing
  – Early 2002-3 season: prevalence of influenza in children with acute respiratory symptoms or fever = 5%
    • PPV = 50%; NPV = 98%
  – Later 2002-3: prevalence = 21%
    • PPV = 85%; NPV = 91%
Predictive values for clinical rapid influenza tests

PPV 2002-2003

NPV 2002-2003

PPV 2003-2004

NPV 2003-2004
Rapid influenza tests-5
Conclusions-1

• Rapid influenza testing is moderately accurate when compared to gold-standard detection (culture/RT-PCR)
  – Sensitivity = 65%; specificity = 97%
• Clinical use of rapid influenza testing requires an estimate of the probability of infection in the patient to be tested
  – Background prevalence in community
  – Patient characteristics
Rapid influenza tests-6

Conclusions-2

• If probability of influenza is low, rapid testing is unlikely to be useful
  – Positive test has high false positive rate
  – Negative test is accurate, but probability of influenza was low anyway

• If probability of influenza is high, rapid testing is unlikely to be useful
  – Positive test is accurate, but probability of influenza was high anyway
  – Negative test has high false negative rate
Rapid influenza tests-7
Conclusions-3

• Best use of rapid influenza test: tie-breaker during periods of moderate prevalence + unique circumstances
  – Unimmunized child
  – Chronic illness
  – Prescription of antiviral medication

• Source of prevalence information
  – http://www.cdc.gov/flu/weekly/fluviewinteractive.htm
FluView Influenza-Like Illness Activity Mobile Application

Download it free from the App Store today
Influenza extras

• Vanderbilt Children’s Clinic and ED
  – 2002-2004
  – Children < 5 years with fever or ARI

• Changes in clinical management: rapid influenza test vs no rapid test
  – ED: marginally fewer other diagnostic tests
  – Clinic: no change in diagnostic testing
  – No difference in use of antibiotics
  – No difference in use of antivirals

• Arch Pediatr Adolesc Med 2006;160:713-718
Interpretation of laboratory tests

Further Reading

- Sackett DL. *Clinical Epidemiology. A basic science for clinical medicine* (2nd ed.) 1991; Boston: Little Brown
- Center for Evidence-Based Medicine — www.cebm.net
Treating infant colic with probiotic *Lactobacillus reuteri*: double blind, placebo controlled randomised trial

- Sung V, Hiscock H, Tang MLK, et al
- Royal Children’s Hospital, Victoria
- BMJ 2014;348:g2107 doi: 10.1136/bmj.g2107
Probiotics and colic-1
Methods-1

• Phase III, double blind, randomized, placebo controlled trial.

• Patients recruited from hospital ED, outpatient clinic, mother-infant parenting center, universal nurse health checks, and private practices.
Probiotics and colic-2
Methods-2

• Inclusion
  – Healthy term infants < 13 weeks of age.
  – Infant colic (Wessel’s criteria of crying or fussing ≥ 3 hours/day for ≥3 out of 7 days: *Pediatrics* 1954;14:421)
  – “Fussing” = “behavior that is not quite crying but not awake and content either.” (Arch Dis Child 1988;63:380)
  – Dairy, non-dairy, and breast feeding all enrolled.
Probiotics and colic-3
Methods-3

• Exclusion
  – Birth weight < 2500 gm.
  – Failure to thrive.
  – Major medical problems.
  – Allergy to cow’s milk protein.
  – On antibiotics or probiotics.
  – Breast-fed babies whose mothers were taking probiotics.
Probiotics and colic-4
Methods-4

• Intervention
  – *L. reuteri*, 0.2 x 10^8 cfu/drop in oil suspension: 5 drops given once daily, OR
  – Placebo in same oil suspension.
  – Duration: 1 month.

• Outcomes
  – Primary: daily cry/fuss time (min/day) recorded in validated home diary.
  – Secondary: infant sleep, maternal mental health and infant/family functioning scores.
Probiotics and colic-5
Methods-5

• Sample size
  – N = 160 provided 80% power to detect minimum effect size of 0.5 standard deviations difference in mean daily cry/fuss time with p <0.05 allowing for dropout rate of 20%.

• “Power” = the ability to detect an effect if present.
Probiotics and colic-6
Results-1

Assessed for eligibility (n=521)

Excluded (n=354): Not meeting inclusion criteria (n=192) Declined to participate (n=162)

Randomised (n=167)

Allocated to probiotic (n=85) Received allocated intervention (n=85)

Allocated to placebo (n=82) Received allocated intervention (n=82)

1 month follow-up

Lost to follow-up (no diary) (n=2)
Discontinued intervention (n=15):
- Infant more unsettled (n=2)
- Infant getting better (n=1)
- Infant constipated (n=1)
- No reason given (n=11)

Primary outcome analysed (n=67)
- Excluded from analysis (<70% diary completion) (n=16)
- Secondary outcomes analysed (n=79)
  - Questionnaire not returned (n=6)

6 month follow-up

Lost to follow-up (no questionnaire) (n=16)
Secondary outcomes analysed (n=65)
- Excluded from analysis (<70% diary completion) (n=4)

Lost to follow-up (no questionnaire) (n=19)
Secondary outcomes analysed (n=58)
- Excluded from analysis (<70% diary completion) (n=5)
Probiotics and colic-7

Results-2

Mean time (95% CI) (min/day)

- **Probiotic**
- **Placebo**

Days of intervention

Fussing

Crying
Probiotics and colic-8
Results-3

• Secondary Outcomes
  – The two groups were similar on all secondary outcomes at 1 and 6 months.
  – Laboratory analysis of fecal samples at 1 month showed no differences between groups in microbial diversity, calprotectin levels, or *E coli* loads.
Probiotics and colic-9
Comparison to other randomized controlled trials

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Probiotic</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Savino 2007</td>
<td>81.70</td>
<td>38.08</td>
</tr>
<tr>
<td>Savino 2010</td>
<td>111.20</td>
<td>335.01</td>
</tr>
<tr>
<td>Szajewska 2013</td>
<td>75.60</td>
<td>9.91</td>
</tr>
<tr>
<td>Sung 2014</td>
<td>217.20</td>
<td>129.50</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=912.25, \, \nu=16.09, \, df=3, \, P=0.001, \, I^2=81\%$

Test for overall effect: $z=2.57, \, P=0.01$
Probiotics and colic-10
Reason for divergent results?

- Sample size was larger in this trial.
- This trial had adequate blinding.
- This trial had adequate randomization.
- This trial used validated home diary vs. interview recall.
- Baseline gut flora in Australia might differ from that in Italy or Poland.
- Other trials used a dairy-free diet.
Conclusions

• The best clinical trial (this one!) showed no benefit from the use of *L. reuteri* in altering the pattern of infant colic.

• A meta-analysis of published trials suggests that probiotics may diminish crying/fussiness by up to 48 min daily.

• Currently there are at least 5 other similar trials taking place worldwide.

• Hang on for the answer.
Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation: a randomized clinical trial

- Aldo Moro University of Bari, Italy
- JAMA Pediatrics 2014;168:228-233
Prophylactic probiotics-1

Methods-1

• Prospective, multicenter, double-blind placebo-controlled, randomized trial.
• Recruitment at 9 Italian pediatric units.
• Inclusion
  – GA > 37 weeks.
  – Normal birth weight.
  – Apgar > 8 at 10 min.
  – Age < 1 week.
  – No chronic illnesses.
Prophylactic probiotics-2
Methods-2

• Intervention
  – *L. reuteri*, 0.2 x 10^8 cfu/drop in oil suspension: 5 drops given once daily for 90 days, OR
  – Placebo in same oil suspension.

• Outcome
  – Episodes of regurgitation, duration of inconsolable crying, numbers of bowel movements recorded using structured home diary.
Prophylactic probiotics-3
Methods-3

• “Regurgitation” = passage of refluxed gastric contents into oral pharynx.
• “Inconsolable crying” = crying ≥ 3 hours/day for ≥3 out of 7 days.
• Data recorded from day of recruitment to 3 months of age.
589 Newborns assessed for eligibility

35 Parents refused participation

554 Neonates randomized

276 Neonates randomized to receive *Lactobacillus reuteri*

- 38 Neonates lost to follow-up
  - 18 Withdrawn by investigator for protocol violation
  - 3 Moved from area
  - 11 Withdrawn by parent
  - 6 Withdrawn by investigator for use of drugs

238 Neonates included in primary analysis

278 Neonates randomized to receive placebo

- 48 Neonates lost to follow-up
  - 1 Withdrawn by investigator for protocol violation
  - 6 Moved from area
  - 13 Withdrawn by parent
  - 8 Withdrawn by investigator for use of drugs

230 Neonates included in primary analysis
### Table 2. Primary Outcome at 1 Month of Life

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) [95% CI]</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Lactobacillus reuteri DSM 17938</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colic, min/d</td>
<td>45 (12) [43.5-46.5]</td>
<td>96 (34) [91.6-100.4]</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Regurgitation, No./d</td>
<td>2.7 (1.5) [2.5-2.9]</td>
<td>3.3 (2.3) [3.0-3.6]</td>
<td>.35</td>
</tr>
<tr>
<td>Evacuation, No./d</td>
<td>4.01 (1.1) [3.9-4.1]</td>
<td>2.8 (0.6) [2.7-2.9]</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

### Table 3. Primary Outcome at 3 Months of Life

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) [95% CI]</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Lactobacillus reuteri DSM 17938</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colic, min/d</td>
<td>37.7 (33.8) [33.4-42.0]</td>
<td>70.9 (51.9) [64.2-77.6]</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Regurgitation, No./d</td>
<td>2.9 (1.1) [2.7-3.0]</td>
<td>4.6 (3.2) [4.2-5.0]</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Evacuation, No./d</td>
<td>4.2 (1.8) [4.0-4.4]</td>
<td>3.6 (1.8) [3.4-3.8]</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• In an adequately powered study, the daily administration of \textit{L. reuteri} decreased the reported incidence of inconsolable crying, regurgitation, and functional constipation in the first 3 months of life.
Probiotics and infant colic. Still a hammer in search of a nail

- Bennett WE.
- Indiana University School of Medicine
- *BMJ 2014;348:g2286.*
Probiotics and colic editorial-1

• The Sung and Indrio articles—both of which constitute the best evidence to date—assessed two different clinical questions
  – Indrio: “Should we give probiotics to all infants to help prevent fussiness/colic?”
  – Sung: “Should we give probiotics to infants with colic to improve their symptoms?”
• Morris Green coined the term “the vulnerable child syndrome” to describe the deleterious effect of a perceived threat to a child’s life through labeling a child “ill.” (Pediatrics 1964;34:58)

• Tarini showed that labeling a normal, benign process as a “disease’ has a substantial impact on parent’s expectation of treatment. (Pediatrics 2013;131:839)
Probiotics and colic editorial-3

• “We should be careful not to walk the same road with probiotics and colic.”
• “A great deal of accumulated clinical experience tells us that children with colic incur no serious long term effects and that symptoms abate with time.”
• The better approach would be: “reassurance, family social support, and tincture of time.”
Five probiotic drops a day to keep infantile colic away?

- Chumpitazi BP, Shulman RJ.
- Baylor College of Medicine
- *JAMA Pediatrics* 2014;168:204-205
A systematic review in 2013 showed insufficient evidence to support the general use of probiotics in all infants with colic. (Sung V. JAMA Pediatr 2013;167:1150)

Indrio et al. in their large, multicenter trial took a preventative approach.

Their results are encouraging.
“Despite their lack of information about the mechanisms of action and some study limitations, Indrio et al lend additional support to the potential use of *L. reuteri* for infantile colic. Perhaps there will come a time when medical providers will recommend 5 probiotic drops a day to keep infantile colic away.”
Article 1
Dipstick screening for urinary tract infection in febrile infants

- Glissmeyer EW, Korgenski EK, Wilkes J, et al
- University of Utah School of Medicine
- *Pediatrics 2014’;133:e1121-e1127*
Dipstick screening for UTI-1
Methods-1

• Retrospective observational study.
• 23 Intermountain Healthcare hospitals.
• Inclusion
  – Febrile infants aged 1-90 days; 2004-2011.
  – Catheterized urine specimens obtained.
• All had urine dipstick, microscopic UA, urine culture.
Dipstick screening for UTI-2
Methods-2

• (+) UTI = ≥ 1 urine pathogen, each ≥50,000 cfu/ml.

• (-) UTI = <10,000 cfu/ml of organisms identified as skin or GU flora.

• (+/-) UTI = 10,000 – 49,999 cfu/ml of urine pathogen.

• Equivocal UTI were excluded from analysis.
Dipstick screening for UTI-3

Methods-3

• (+) Dipstick = either LE (+) or NIT (+). (+) = > “trace.”

• (+) Micro = >10 WBC/hpf or any bacteria seen.

• Sensitivity, specificity, PPV, NPV were calculated for each of the UA results.
Dipstick screening for UTI-4
Results-1

• 13,030 febrile infant encounters.
• 6536/13,030 (50%) had all urine studies
• After equivocal UCx excluded, 6394 enrolled infants were analyzed.
• 770/6394 (prevalence = 12%) had (+) UTI.
Dipstick screening for UTI-5
Results-2

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90.8</td>
<td>93.8</td>
<td>66.8</td>
<td>98.7</td>
</tr>
</tbody>
</table>

Sensitivity Specificity PPV NPV
Dipstick screening for UTI-6
Results-3

• Likelihood Ratios
  – (-) Dipstick = 0.1.

• Urine microscopy did not add any meaningful accuracy to dipstick alone.

• False positive screens were higher with urine microscopy: 8 infants had false positive micro testing for every 1 infant with true UTI not identified by dipstick.
Likelihood Ratio

• The Likelihood Ratio (LR) is the odds that a given test result would be expected in a patient with the target disorder compared to the likelihood that that same result would be expected in a patient without the target disorder.

• References

• Explanation and examples

• Compute likelihood ratios
  – http://araw.med.e.uic.edu/cgi-bin/testcalc.pl
Effect of prevalence on predictive value
Likelihood Ratio

- http://araw.medec.uic.edu/cgi-bin/testcalc.pl
Dipstick screening for UTI-7
Results-4

• Fate of infants with (-) dipstick but (+) UCx
  – Age 1-28 days:
    • All febrile neonates were admitted to hospital with full sepsis workup and antibiotics.
  – Age 29-90 days (53 febrile infants):
    • 83% were admitted to hospital anyway and started on effective antibiotics.
    • 17% were sent home. All had (+) UCx by 24 hours and were treated with antibiotics.
    • Two (3.8%) had bacteremia; none had (+) CSF.
Dipstick screening for UTI-8

Conclusions

• These data comprise the largest study of urinary diagnostic testing in febrile infants < 90 days.

• No urine screening test has perfect accuracy.

• The use of urine dipstick testing alone, without microscopy, is an effective screening tool.

• Dipstick testing + use of likelihood ratios can enhance decision-making.
A new technique for fast and safe collection of urine in newborns

- Fernandez MLF, Merino NG, Garcia AT et al.
- University Infanta Sofia Hospital, Madrid
- *Arch Dis Child* 2013;98:27-29
Urine collection-2
Methods

• Prospective feasibility and safety study.
• Inclusion: infants ≤ 1 month who required a urine sample
• Technique: feed the baby; 25 min later, clean genitals; hold baby under armpits with legs dangling; rapid tapping on bladder for 30 sec; light circular massage of lumbar paravertebral zone for 30 sec; repeat until micturition
Urine collection-3

Results

- 80 consecutive infants: 31 girls and 49 boys; mean age 6 days.
- 86% success rate
- Mean time for sample collection was 57 sec. No difference between genders.
- Controlled crying occurred in all babies
Urine collection-4
Conclusions

• Midstream urine collection in infants is possible with minimum trauma 86% of the time.
Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months

• Subcommittee on Urinary Tract Infection
• Roberts KB, Chair
• American Academy of Pediatrics
• *Pediatrics* 2011;128:595-610
UTI-guideline-2
Methods-1

• Two comprehensive literature searches for published studies < 10 years.
• Authors of studies who provided insufficient data detail contacted.
• Meta-analyses performed
• Results provided to committee members with discussion until “consensus” reached (not defined)
### UTI-guideline-3

**Strength of recommendations**

<table>
<thead>
<tr>
<th>Evidence Quality</th>
<th>Preponderance of Benefit or Harm</th>
<th>Balance of Benefit and Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Well designed RCTs or diagnostic studies on relevant population</td>
<td>Strong Recommendation</td>
<td>Option</td>
</tr>
<tr>
<td>B. RCTs or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies</td>
<td>Recommendation</td>
<td>Option</td>
</tr>
<tr>
<td>C. Observational studies (case-control and cohort design)</td>
<td></td>
<td>No Rec</td>
</tr>
<tr>
<td>D. Expert opinion, case reports, reasoning from first principles</td>
<td>Option</td>
<td></td>
</tr>
<tr>
<td>X. Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit or harm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. Strong: A catheterized UCx and UA should be obtained for all infants with fever-without-source ill enough to be given immediate antibiotics. (Evidence quality A)
2. Strong: If the febrile infant does not require immediate antibiotics, then the likelihood of UTI should be determined. (Evidence quality A)
UTI-guideline-5
Recommendations-2

a. Low likelihood: follow-up without testing

b. “Not-low-likelihood”:
   1. catheterized urine for culture and analysis
   2. “Clean catch” urine for UA; if LE (+) or Nitrite (+) or Micro (+), then catheterized for UCx; if (-), then follow.
### Individual Risk Factors: Girls

- White race
- Age < 12 mo
- Temperature ≥ 39°C
- Fever ≥ 2 d
- Absence of another source of infection

### Probability of UTI vs. No. of Factors Present

<table>
<thead>
<tr>
<th>Probability of UTI</th>
<th>No. of Factors Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1%</td>
<td>No more than 1</td>
</tr>
<tr>
<td>≤2%</td>
<td>No more than 2</td>
</tr>
</tbody>
</table>

### Individual Risk Factors: Boys

- Nonblack race
- Temperature ≥ 39°C
- Fever > 24 h
- Absence of another source of infection

### Probability of UTI vs. No. of Factors Present

<table>
<thead>
<tr>
<th>Probability of UTI</th>
<th>Uncircumcised</th>
<th>Circumcised</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1%</td>
<td>a</td>
<td>No more than 2</td>
</tr>
<tr>
<td>≤2%</td>
<td>None</td>
<td>No more than 3</td>
</tr>
<tr>
<td>Test</td>
<td>Sensitivity (Range), %</td>
<td>Specificity (Range), %</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Leukocyte esterase test</td>
<td>83 (67–94)</td>
<td>78 (64–92)</td>
</tr>
<tr>
<td>Nitrite test</td>
<td>53 (15–82)</td>
<td>98 (90–100)</td>
</tr>
<tr>
<td>Leukocyte esterase or nitrite test positive</td>
<td>93 (90–100)</td>
<td>72 (58–91)</td>
</tr>
<tr>
<td>Microscopy, WBCs</td>
<td>73 (32–100)</td>
<td>81 (45–98)</td>
</tr>
<tr>
<td>Microscopy, bacteria</td>
<td>81 (16–99)</td>
<td>83 (11–100)</td>
</tr>
<tr>
<td>Leukocyte esterase test, nitrite test, or microscopy positive</td>
<td>99.8 (99–100)</td>
<td>70 (60–92)</td>
</tr>
</tbody>
</table>
3. Recommended: A UTI = both abnormal UA and $\geq 50,000$ cfu/ml of a uropathogen on catheterized specimen. (Evidence quality C)

4. Strong: Oral and parenteral antibiotics are equally efficacious. (Evidence quality A)

5. Recommendation: Treatment duration = 7-14 days. (Evidence quality B)
5. Recommended: Febrile infants with UTIs should have renal and bladder ultrasonography (Evidence quality C)

6. Recommended: VCUG should not be performed routinely after 1\textsuperscript{st} febrile UTI unless US study suggests high-grade reflux or obstruction. (Evidence quality B)

a. Recurrent UTI, perform VCUG. (Evidence quality X)
VCUG or no?

• “If prophylaxis is, in fact, not beneficial and VUG is not required for development of pyelonephritis, then the rationale for performing VCUG routinely must be questioned.”

### Table 4

<table>
<thead>
<tr>
<th>Reflux Grade</th>
<th>Prophylaxis</th>
<th>No. of Recurrences</th>
<th>Total N</th>
<th>No Prophylaxis</th>
<th>No. of Recurrences</th>
<th>Total N</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>7</td>
<td>210</td>
<td></td>
<td>11</td>
<td>163</td>
<td></td>
<td>.15</td>
</tr>
<tr>
<td>I</td>
<td>2</td>
<td>37</td>
<td></td>
<td>2</td>
<td>35</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>133</td>
<td></td>
<td>10</td>
<td>124</td>
<td></td>
<td>.95</td>
</tr>
<tr>
<td>III</td>
<td>31</td>
<td>140</td>
<td></td>
<td>40</td>
<td>145</td>
<td></td>
<td>.29</td>
</tr>
<tr>
<td>IV</td>
<td>16</td>
<td>55</td>
<td></td>
<td>21</td>
<td>49</td>
<td></td>
<td>.14</td>
</tr>
</tbody>
</table>
**Antibiotic prophylaxis**

**Meta-analyses: 0-Gr IV reflux**

**A**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antimicrobial Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craig et al (2006)</td>
<td>1</td>
<td>10</td>
<td>12</td>
<td>49.9%</td>
<td>1.20 (0.99-1.64)</td>
</tr>
<tr>
<td>Garin et al (2006)</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Montini et al (2008)</td>
<td>1</td>
<td>15</td>
<td>18</td>
<td>50.1%</td>
<td>0.53 (0.04-7.44)</td>
</tr>
<tr>
<td>Roussé-Kesler et al (2008)</td>
<td>0</td>
<td>7</td>
<td>0 &amp; 2</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>37</td>
<td>35</td>
<td>72</td>
<td>100.0%</td>
<td>0.80 (0.12-5.46)</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

**B**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antimicrobial Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craig et al (2009)</td>
<td>1</td>
<td>27</td>
<td>28</td>
<td>6.3%</td>
<td>0.29 (0.03-6.69)</td>
</tr>
<tr>
<td>Garin et al (2006)</td>
<td>1</td>
<td>12</td>
<td>13</td>
<td>6.5%</td>
<td>2.54 (1.11-56.25)</td>
</tr>
<tr>
<td>Montini et al (2008)</td>
<td>3</td>
<td>31</td>
<td>34</td>
<td>21.7%</td>
<td>0.87 (0.18-4.73)</td>
</tr>
<tr>
<td>Pennesi et al (2008)</td>
<td>1</td>
<td>11</td>
<td>12</td>
<td>6.5%</td>
<td>2.79 (0.12-60.70)</td>
</tr>
<tr>
<td>Roussé-Kesler et al (2008)</td>
<td>6</td>
<td>32</td>
<td>38</td>
<td>59.0%</td>
<td>1.04 (0.37-2.90)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>133</td>
<td>124</td>
<td>257</td>
<td>100.0%</td>
<td>1.04 (0.47-2.29)</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>11</td>
<td>10</td>
<td>21</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

**C**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antimicrobial Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craig et al (2009)</td>
<td>6</td>
<td>28</td>
<td>34</td>
<td>35.0%</td>
<td>0.41 (0.16-1.01)</td>
</tr>
<tr>
<td>Garin et al (2009)</td>
<td>3</td>
<td>10</td>
<td>13</td>
<td>14.8%</td>
<td>1.20 (0.26-5.53)</td>
</tr>
<tr>
<td>Pennesi et al (2008)</td>
<td>8</td>
<td>17</td>
<td>25</td>
<td>50.2%</td>
<td>0.94 (0.47-1.90)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>55</td>
<td>49</td>
<td>104</td>
<td>100.0%</td>
<td>0.73 (0.39-1.35)</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>16</td>
<td>21</td>
<td>37</td>
<td>22%</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.07, df = 2 (P = 0.85); P = 0%

Test for overall effect: $z = 1.01 (P = .31)$
Prophylactic antibiotics?

• Meta-analyses show no significant reduction in symptomatic UTI regardless of VUR.
  – *Arch Dis Child* 2010;95:499-508

• The 1 study that showed benefit: absolute risk reduction for symptomatic UTI over 1 year was only 6%.

• “If UTI prophylaxis worked, it would offer us the chance to treat 16 children with antibiotics for a year to prevent treating one child with antibiotics for a week.”
  – *Pediatrics* 2011;128:572-575
Section on Urology response to new guidelines

• Executive Committee, Section on Urology (SOU)
• American Academy of Pediatrics
• *Pediatrics* 2012;129:e1051-e1053
Urologist response-2

• “Some” aspects of new guidelines supported, but new recommendation not to perform VCUG is not supported.

• “The section expresses significant concern that the recommendation is based on a flawed interpretation of limited data and that this stands to potentially harm significant numbers of children because of delayed diagnosis of harmful urinary tract conditions.”
Urologist response-3

• The meta-analytic combination raises concerns regarding the validity of the conclusions as well.
• Some individual studies actually show a small trend toward antibiotic efficacy.
• When combined, however, the overall effect disappears.
• This possibly reflects “amalgamation effect” (Simpson’s paradox)
Edward H. Simpson’s Paradox
Admission to UC Berkeley-1973

<table>
<thead>
<tr>
<th></th>
<th>Applicants</th>
<th>Admitted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td>8442</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>4321</td>
<td>35%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Department</th>
<th>Men Applicants</th>
<th>Men Admitted</th>
<th>Women Applicants</th>
<th>Women Admitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>825</td>
<td>62%</td>
<td>108</td>
<td>82%</td>
</tr>
<tr>
<td>B</td>
<td>560</td>
<td>63%</td>
<td>25</td>
<td>68%</td>
</tr>
<tr>
<td>C</td>
<td>325</td>
<td>37%</td>
<td>593</td>
<td>34%</td>
</tr>
<tr>
<td>D</td>
<td>417</td>
<td>33%</td>
<td>375</td>
<td>35%</td>
</tr>
<tr>
<td>E</td>
<td>191</td>
<td>28%</td>
<td>393</td>
<td>24%</td>
</tr>
<tr>
<td>F</td>
<td>272</td>
<td>6%</td>
<td>341</td>
<td>7%</td>
</tr>
</tbody>
</table>
Response to the AAP Section on Urology concerns

- Roberts KB, Fennell ME, Downs SM.
- University of North Carolina and Indiana University Schools of Medicine
- Pediatrics 2012;129:e1054-e1056
Response to Urologists-2

- We agree:
  - Some of the data are from studies using bag specimens.
  - Uncircumcised status may increase the risk of recurrent UTI or false-positive cultures.
  - Bowel and bladder habits can have a marked influence on the incidence of UTI.

- But:
  - Intention-to-treat analysis used here is the preferred approach to possible noncompliance.
Response to Urologists-3

– The small number of subjects in the individual studies is precisely the reason meta-analysis was used.

• Simpson’s Paradox does not apply:
  – There was no reversal of the direction of the effect but a narrowing of the confidence interval around an effect that is consistent across studies.
  – The small number of subjects in the individual studies is precisely the reason meta-analysis was used.
Antibiotic prophylaxis

Meta-analyses: 0-Gr IV reflux

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antimicrobial</th>
<th>Control</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craig et al (2009)</td>
<td>1</td>
<td>10</td>
<td>12</td>
<td>49.9%</td>
<td>1.20</td>
<td>0.09–16.64</td>
<td></td>
</tr>
<tr>
<td>Garin et al (2006)</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>Not estimable</td>
<td>0.53</td>
<td>0.04–7.44</td>
<td></td>
</tr>
<tr>
<td>Montini et al (2008)</td>
<td>1</td>
<td>15</td>
<td>1</td>
<td>50.1%</td>
<td>0.53</td>
<td>0.04–7.44</td>
<td></td>
</tr>
<tr>
<td>Roussy-Kesler et al (2008)</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>Not estimable</td>
<td>0.53</td>
<td>0.04–7.44</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>37</td>
<td>35</td>
<td></td>
<td>100%</td>
<td>0.80</td>
<td>0.12–5.16</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0.00$; $X^2 = 1.08$, $df = 1$ ($P = .31$); $P = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 0.24$ ($P = .81$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antimicrobial</th>
<th>Control</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craig et al (2009)</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td>100%</td>
<td>0.39</td>
<td>0.06–2.33</td>
<td></td>
</tr>
<tr>
<td>Garin et al (2006)</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>Not estimable</td>
<td>0.59</td>
<td>0.24–1.41</td>
<td></td>
</tr>
<tr>
<td>Montini et al (2008)</td>
<td>1</td>
<td>15</td>
<td>1</td>
<td>50.1%</td>
<td>1.40</td>
<td>0.63–3.12</td>
<td></td>
</tr>
<tr>
<td>Roussy-Kesler et al (2008)</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>Not estimable</td>
<td>0.70</td>
<td>0.29–1.64</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>31</td>
<td>40</td>
<td></td>
<td>100%</td>
<td>0.75</td>
<td>0.40–1.40</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>31</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0.27$; $X^2 = 9.54$, $df = 5$ ($P = .09$); $P = 48%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 0.50$ ($P = .37$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antimicrobial</th>
<th>Control</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craig et al (2009)</td>
<td>0</td>
<td>27</td>
<td>1</td>
<td>6.3%</td>
<td>0.29</td>
<td>0.03–6.69</td>
<td></td>
</tr>
<tr>
<td>Garin et al (2006)</td>
<td>1</td>
<td>12</td>
<td>0</td>
<td>6.5%</td>
<td>2.54</td>
<td>0.11–66.25</td>
<td></td>
</tr>
<tr>
<td>Montini et al (2008)</td>
<td>3</td>
<td>31</td>
<td>2</td>
<td>21.7%</td>
<td>0.37</td>
<td>0.16–4.73</td>
<td></td>
</tr>
<tr>
<td>Pennesi et al (2008)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>6.5%</td>
<td>2.75</td>
<td>0.12–60.70</td>
<td></td>
</tr>
<tr>
<td>Roussy-Kesler et al (2008)</td>
<td>0</td>
<td>32</td>
<td>0</td>
<td>Not estimable</td>
<td>1.04</td>
<td>0.37–3.20</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>133</td>
<td>124</td>
<td></td>
<td>100%</td>
<td>1.04</td>
<td>0.47–2.39</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>11</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0.00$; $X^2 = 1.38$, $df = 4$ ($P = .85$); $P = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 0.10$ ($P = .92$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Response to Urologists-4

– Simpson’s Paradox occurs when data analyzed in separate strata yield different results; here they were consistent.

– The Mantel-Haenzel method used here for statistical significance avoids the Simpson paradox.

• We are pleased that the SOU is actively engaged in research.

• Without evidence to the contrary: primum non nocere.