OR, CHECKING OUT HOT BABES
OBJECTIVES

• Understand the challenge of treating fever in infants
• Evaluate the application of traditional protocols in today’s management
• Identify newer protocols seeking to identify infants at low risk for bacterial infection
OUR SCOPE

- Infants < 3 months
- Term
- Otherwise healthy
- Well-appearing
- Initial encounter

It’s a boy!

45 days old
Born at 39 weeks by NSVD
No prolonged hospital stay
Received HBV#1 in the hospital
Exclusively breastfed, growing well
WHY ARE WE SO CONCERNED ABOUT FEVERS?

UNRELIABLE
WHY ARE WE SO CONCERNED ABOUT WORKUP?

Morbidity of workup
- Hospital stays
- Invasive procedures

Long-term risks of early antibiotic use
- Individual
- Community

Costs of hospitalization
OUTCOMES ASSOCIATED WITH EARLY ANTIBIOTIC EXPOSURE

Animal studies
- Increased anxiety and change in social behaviors

Associations in human studies
- Obesity and metabolic syndrome
- Inflammatory bowel disease
- Celiac disease
- Autoimmune disease

Antibiotic Use in First 2 Years

- Antibiotics: 70%
- No antibiotics: 30%
ETIOLOGY OF FEVER IN INFANTS

- **Viral**
  - RSV
  - Influenza
  - Adenovirus
  - Enterovirus
  - HSV
- **Local Bacterial**
  - UTI
  - Cellulitis
  - Osteomyelitis
  - Gastroenteritis
  - Pneumonia
- **Invasive Bacterial**
  - Bacteremia
  - Meningitis

35% Viral
13-20% Local Bacterial
1% Invasive Bacterial
PUBLIC HEALTH INTERVENTIONS

- Hib vaccine
  - 20,000 cases annually in 1970s
  - 30 cases in 2008
- PCV 13
  - 17,000 cases annually invasive pneumococcal disease <5 y/o
  - 95% reduction in IPD with vaccination
- GBS screening/prophylaxis
  - Active surveillance starts 1990
  - 80% decline in early onset GBS
Annual trends in invasive pneumococcal disease among children <5 years old, United States, 2006-2013

NVT: non-vaccine serotypes; PCV7: serotypes included in the 13-valent pneumococcal conjugate vaccine that are not included in the 7-valent pneumococcal vaccine, excluding serotype 6A (1, 5, 3, 7F, 19A); PCV7+6A: serotypes in the 7-valent pneumococcal conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F) plus serotype 6A (for which serotype 6B antigen provides cross-protection); IPD: invasive pneumococcal disease.

Rochester Criteria
Reassuring if all criteria are present

Well appearing infant

No skeletal, soft tissue, skin or ear infections

Full term birth

No prior illness
- No prior hospitalizations
- Not hospitalized longer than mother after delivery
- No prior antibiotics
- No Hyperbilirubinemia
- No chronic or underlying illness

Complete Blood Count normal
- White Blood Cell Count normal (5000 to 15,000/mm3)
- Band Neutrophils < 1,500/mm3

Other Lab Findings
- If Diarrhea is present, Fecal Leukocytes < 5 WBC/hpf
- Urine White Blood Cells < 10 WBC/hpf
BOSTON CRITERIA - 1992

• Age range: 28-89 days

• Low-risk criteria:
  • Clinical appearance
  • Lab values including CSF analysis

• Intervention:
  • All infants deemed low-risk received IM ceftriaxone, discharged home
  • Follow up with scheduled phone calls, repeat evaluation within 24 hours for 2nd ceftriaxone dose

• Findings:
  • 94.6% negative predictive value for SBI in low-risk infants
  • 453 of patients without SBI avoided hospitalization
PHILADELPHIA CRITERIA - 1993

- Age range: 29-60 days
- Low risk criteria:
  - Clinical appearance (Infant Observation Score)
  - Lab values including CSF analysis
- Management:
  - High risk – empiric antibiotics and admission for any positive screen
  - Low risk – randomized to outpatient observation vs inpatient observation, without antibiotics
- Findings:
  - 98% sensitivity using initial screening, 42% specificity
  - 100% sensitivity with inclusion of band to neutrophil ratio
  - Infant Observation Score alone not predictive of SBI
  - Estimated savings of $435,000
<table>
<thead>
<tr>
<th></th>
<th>Rochester</th>
<th>Boston</th>
<th>Philadelphia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age range</strong></td>
<td>≤60 days</td>
<td>28-89 days</td>
<td>29-60 days</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>≥38°C</td>
<td>≥38°C</td>
<td>≥38.2°C</td>
</tr>
</tbody>
</table>
| **History**        | Term
No perinatal antibiotics
No underlying disease
Not hospitalized longer than mom
No immunizations within the past 48 hours
No antimicrobial within 48 hours
Not dehydrated | No immunizations within the past 48 hours
No antimicrobial within 48 hours
Not dehydrated | No specifications |
| **Lab parameters** | CSF: N/A
WBC >5000 and <15,000/mm³
ABC <1500
UA ≤10 WBCs/hpf
Stool (+/-): ≤5 WBCs/hpf | CSF with WBC <10/mm³
WBC <20,000/mm³
UA <10 WBCs/hpf
Chest radiograph: no infiltrate (if obtained) | CSF with WBC <8/mm³
WBC <15,000/mm³
UA <10 WBCs/hpf
Urine Gram stain negative
CSF Gram stain negative
CXR: no infiltrate
Stool (+/-): no blood, few or no WBCs on smear
Band-neutrophil ratio <0.2 |
| **Management for low risk** | **Home/outpatient**
No antibiotics*
Follow-up required | **Home/outpatient**
Empiric antibiotics
Follow-up required | **Home/outpatient**
No antibiotics
Follow-up required |
# Low Risk Criteria

<table>
<thead>
<tr>
<th></th>
<th>Rochester</th>
<th>Boston</th>
<th>Philadelphia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>N/A</td>
<td>WBC &lt; 10</td>
<td>WBC &lt; 8, gram stain negative</td>
</tr>
<tr>
<td>CBC</td>
<td>WBC 5-15</td>
<td>WBC &lt; 20</td>
<td>WBC &lt; 15</td>
</tr>
<tr>
<td>Bands</td>
<td>Abs band count &lt; 1500</td>
<td>N/A</td>
<td>Band-neutrophil ratio &lt; 0.2</td>
</tr>
<tr>
<td>UA</td>
<td>≤10 WBC/hpf</td>
<td>&lt;10 WBC/hpf</td>
<td>&lt;10 WBC/hpf, gram stain negative</td>
</tr>
</tbody>
</table>
JASON IN ROCHESTER

Age: 45 days
Temperature: 38.3°C rectally
LP: N/A
WBC: 11,000 with 8% bands
UA: 3 WBC/hpf
No stool studies
No CXR

Rochester

≤60 days
≥38°C
Term
No perinatal antibiotics
No underlying disease
Not hospitalized longer than mom
CSF: N/A
WBC >5000 and <15,000/mm³
ABC <1500
UA ≤10 WBCs/hpf
Stool (+/-): ≤5 WBCs/hpf
Home/outpatient*
No antibiotics*
Follow-up required
JASON IN BOSTON

Age: 45 days
Temperature: 38.3°C rectally
LP: Champagne, no WBC
WBC: 11,000 with 8% bands
UA: 3 WBC/hpf
No stool studies
No CXR

Boston

28-89 days
≥38°C
No immunizations within the past 48 hours
No antimicrobial within 48 hours
Not dehydrated
CSF WBC <10/mm³
WBC <20,000/mm³
UA <10 WBCs/hpf
Chest x-ray: no infiltrate (if obtained)
Home/outpatient
Empiric antibiotics
Follow-up required
JASON IN PHILADELPHIA

Age: 45 days
Temperature: 38.3°C rectally
LP: Champagne, no WBC
WBC: 11,000 with band-neutrophil ratio 0.18
UA: 3 WBC/hpf
No stool studies
No CXR

Philadelphia

28-60 days
≥38.2°C
No specific history
CSF WBC <8/mm³
WBC <15,000/mm³
UA <10 WBCs/hpf
Urine Gram stain negative
CSF Gram stain negative
CXR: no infiltrate
Stool (+/-): no blood, few or no WBCs on smear
Band-neutrophil ratio <0.2
Home/outpatient
No antibiotics
Follow-up required
<table>
<thead>
<tr>
<th>Age/Appearance</th>
<th>Recommendation</th>
<th>Cases in Which Guideline Was Followed, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;31 days</td>
<td>Complete sepsis workup/hospitalization/antibiotics</td>
<td>45.7</td>
</tr>
<tr>
<td>31-90 days/mildly or moderately ill</td>
<td>Complete sepsis workup/hospitalization/antibiotics</td>
<td>35.8</td>
</tr>
<tr>
<td>31-90 days/minimally ill</td>
<td>White blood cell count/urinalysis</td>
<td>41.6</td>
</tr>
</tbody>
</table>

Abbreviation: PROS, Pediatric Research in Office Settings.

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**APPLICATION OF GUIDELINES 2004**
APPLICATION OF GUIDELINES 2010
62% of respondents reported using some set of published guidelines

- Philadelphia: 20%
- Rochester: 15%
- Boston: 13%
- Baraff: 23%
- Unsure: 12%
- Institutional: 17%
### Deviations from Self-Reported Guidelines

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendations per guideline</th>
<th>Lumbar puncture</th>
<th>Empiric antibiotics</th>
<th>Hospital admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rochester (25 and 44 day old infants)</td>
<td>No LP No antibiotics Discharge</td>
<td>25d - 98% performed 44d – 51% performed</td>
<td>25d - 86% gave 44d – 49% gave</td>
<td>25d - 93% admitted 44d – 12% admitted</td>
</tr>
<tr>
<td>Philadelphia (44 day old infant)</td>
<td>Perform LP No antibiotics Discharge</td>
<td>44% neglected</td>
<td>29% gave</td>
<td>8% admitted</td>
</tr>
<tr>
<td>Boston (44 and 67 day old infants)</td>
<td>Perform LP Give antibiotics Discharge</td>
<td>44d - 28% neglected 67d – 68% neglected</td>
<td>44d - 36% neglected 67d – 60% neglected</td>
<td>44d - 4% admitted 67d – 4% admitted</td>
</tr>
</tbody>
</table>

Table adapted from 2010 Lippincott Williams & Wilkins, figure 3
THE TIMES THEY ARE A-CHANGIN’

1970s Polio, Dtap, MMR

1985 Rochester Criteria

1988 Hib Vaccine

1990 Universal GBS Screening

1992 Boston Criteria

1993 Philadelphia Criteria

2000 PCV7

2010 PCV13
**LAB-SCORE - 2015**

- **Age range:** 7 days – 36 months
- **Low-risk criteria:**
  - Score ≥ 3 is cutoff
- **Intervention:**
  - Not specified (provider discretion)
- **Findings:**
  - 94% sensitivity
  - 81% specificity

### Lab Score

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCT (ng/ml)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.5</td>
<td>0</td>
</tr>
<tr>
<td>0.5-2</td>
<td>2</td>
</tr>
<tr>
<td>≥ 2</td>
<td>4</td>
</tr>
<tr>
<td><strong>CRP (mg/L)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>0</td>
</tr>
<tr>
<td>40-99</td>
<td>2</td>
</tr>
<tr>
<td>≥ 100</td>
<td>4</td>
</tr>
<tr>
<td><strong>Urine dipstick (+LE or NIT)</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
</tr>
<tr>
<td>Positive</td>
<td>1</td>
</tr>
</tbody>
</table>
### Step by Step - 2016

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Positive LR</th>
<th>Negative LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rochester criteria</td>
<td>81.6 (72.2–88.4)</td>
<td>44.5 (42.4–46.6)</td>
<td>5.7 (4.6–7.2)</td>
<td>98.3 (97.3–99.0)</td>
<td>1.47 (1.32–1.64)</td>
<td>0.41 (0.26–0.65)</td>
</tr>
<tr>
<td>Lab-score</td>
<td>59.8 (49.3–69.4)</td>
<td>84.0 (82.4–85.5)</td>
<td>13.4 (10.4–17.2)</td>
<td>98.1 (97.3–98.6)</td>
<td>3.74 (3.07–4.56)</td>
<td>0.48 (0.37–0.62)</td>
</tr>
<tr>
<td>Step by Step</td>
<td>92.0 (84.3–96.0)</td>
<td>46.9 (44.8–49.0)</td>
<td>6.7 (5.4–8.3)</td>
<td>99.3% (98.5–99.7)</td>
<td>1.73 (1.61–1.85)</td>
<td>0.17 (0.08–0.35)</td>
</tr>
</tbody>
</table>
ON THE HORIZON

• Pediatric Emergency Care Applied Research Network (PECARN)
• Infants < 60 days
• 22 emergency departments in the US
• Host expression patterns (RNA biosignatures)
# ONE APPROACH

**Infants < 28 days**

Complete sepsis evaluation:
- CBC
- UA
- CSF analysis
- Blood, urine cultures
- Empiric antibiotics
- Inpatient observation

**Infants 29-90 days**

- Step-by-Step approach if labs available
- Rochester criteria if not
- Draw blood, urine cultures
- Assess caregiver preferences
- Defer antibiotics
- Follow up within 24 hours
SUMMARY

• Traditional guidelines with low threshold for intervention were developed prior to widespread use of multiple public health initiatives

• Ongoing efforts to improve non-invasive identification of low-risk infants

• No consensus guidelines exist for the management of febrile infants
PARTING THOUGHTS

In 1974, senior pediatric residents assigned to the emergency department at Johns Hopkins Children's Center identified management of febrile infants younger than 2 months as one of the clinical problems they found most vexing. The residents believed that their clinical judgment was demeaned by the prevailing notion that all young, febrile infants need a complete evaluation for invasive bacterial disease, regardless of clinical appearance.
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Dr. Belinda Fu
Dr. Frank Bell
Dr. Puja Dalal

The incredible nursing team of First Hill Family Medicine, for ensuring all our kiddos get their vaccines!
REFERENCES


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• Roberts KB. Young febrile infants: A 30-year odyssey ends where it started. JAMA 2004;291:1261-1262 (editorial)
