Bacterial infection in the neonate and young infant: a review
Russell J. McCulloh, MD
Med-Peds Infectious Diseases
August 8, 2017

Disclosures
- I have no financial interests to disclose
- Funding:
  - Eva and Kenneth Smith Foundation
  - Katherine Berry Richardson Foundation
  - Gerber Foundation
  - NIH
  - KCALSI

Goals
- Discuss unresolved issues and common conundrums faced by front-line clinicians in the evaluation of neonatal fever
- Review recent literature on epidemiology and laboratory testing for infants with fever
- Review potential management strategies for febrile infants based on existing and emerging data

Background
- Infants <90 days old with fever can present a diagnostic dilemma
  - HCP see these children on a daily basis
  - Tens of thousands of evaluations/year
  - Small but significant risk of SBI
  - PE & patient history may not be helpful in identifying those with SBI
- SBI: Serious Bacterial Infection
  - Wording changing to just infection types

Definitions
- Serious bacterial infection (SBI)
  - Meningitis
  - Bone and joint infections
  - Pneumonia
  - UTI (disputed if uncomplicated)
  - Sepsis/bacteremia
  - Enteritis

Why Worry about these Infants?
- Most appear WELL
- Unable to clinically distinguish SBI from viral illnesses
- No laboratory test is 100% sensitive/specific for SBI
- Can decline rapidly in face of SBI
- Fever may be only indicator of SBI
### Why the Higher Risk?
- Lower level of immunocompetence
  - Decreased opsonin activity
  - Decreased macrophage function
  - Decreased neutrophil activity
- Poor IgG response to encapsulated bacteria
  - Until >24 months of age

### Challenge: identification
- Initial evaluation of these patients needs to be focused on identifying SBI
  - Research done to help identify infants with SBI
  - Established criteria for low-risk (more later)
  - Evaluation, treatment vary despite published treatment guidelines

### Stratifying to Low Risk

<table>
<thead>
<tr>
<th>Rochester Criteria</th>
<th>Philadelphia Criteria</th>
<th>Boston Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>No source for fever</td>
<td>Observation Score WBC&lt;15,000</td>
<td>WBC&lt;30,000</td>
</tr>
<tr>
<td>Previously healthy</td>
<td>UA&lt;10 WBC/HPF</td>
<td>UA&lt;10 WBC/HPF</td>
</tr>
<tr>
<td>Full term</td>
<td>CSF analysis&lt;8 WBC</td>
<td>CSF analysis&lt;10 WBC</td>
</tr>
<tr>
<td>No prior or current Abx</td>
<td>Normal CXR</td>
<td>Normal CXR</td>
</tr>
<tr>
<td>WBC 5,000-15,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1,500 bands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA&lt;10 WBC/HPF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool &lt;5 WBC/HPF if diarrhea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Pediatric Research in Office Settings Network (PROS): AAP
- Pantell, et al. JAMA 2004, 291 (10) 1203-12
- 3066 infants, <3mos (1995-98), temp 38
  - Included well and ill appearing patients
- 573 members, 219 practices, 44 states(DC,PR)
- SBI = bacteremia, meningitis

### PROS
- 64% (1975) outpt management only
- <1 mo (775): CBC (83%), LP (55%), Abx (68%)
  - 309 not hospitalized (45% adherence to guidelines)
- After hours, Medicaid = more testing
- PROS: Sensitivity 97.1%, Specificity 35.5% (initial antibiotic therapy)
**PROS**

- More less-invasive testing: CBC, UA
- Less more-invasive testing: LP, hospitalized
- 2 kids missed, both <28 days, good outcomes (GBS bacteremia, pneumococcal meningitis)
- Best Prediction Model missed 4 pts (n=1056)
  - Clinically well, >25 days, temp<38.6

**PROS**

- So pediatricians are pretty good at recognizing infants who will have a SBI
- Despite not adhering to the guidelines
- Ongoing relationship with pt, understand caregiver observational skills and reliability

---

**The Conundrum**

- "The clinical dilemma is how to balance the risk of missing an SBI (with potentially a devastating outcome) with the risks and costs associated with diagnostic and management strategies for febrile infants 3 months or younger."—AHRQ

**Questions to Be Addressed**

- What laboratory studies are indicated for various age ranges?
- Which patients need in-depth evaluation and treatment?
- Which patients need treatment with antibiotics?
- Which patients should be hospitalized?
- Which patients can be sent home safely and what follow-up is appropriate for them?

---

**SBI Epidemiology**

- Relatively high prevalence of SBI in young infants
- Incidence of SBI in febrile infants
  - <1 month old → 9 to 14%
  - 1-2 months old → 5 to 9%
- Younger age means higher risk
  - <28 days vs 29-59 days vs 60-89 days

---

**Meningitis risk**

- Prevalence of meningitis:
  - ~1%
  - ~0.4%
**Bacteremia risk**

- Prevalence of bacteremia: ~3%
- Prevalence of bacteremia: ~1.6%

**Bacterial epidemiology across hospitals by source.**


- 8-site review of febrile infant evaluations 7/12-6/14
- 470 infants with bacterial infections: 352 (77%) with UTI alone and 108 (23%) with meningitis or bacteremia

**Utah's Pathogen Profile**


<table>
<thead>
<tr>
<th>Pathogen</th>
<th>N (%)</th>
<th>Resistant to Amp</th>
<th>CTZ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>7 (72)</td>
<td>2 (29)</td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td>6 (19)</td>
<td>6 (100)</td>
<td></td>
</tr>
<tr>
<td>GBS</td>
<td>5 (10)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Salmonella sp</td>
<td>3 (9)</td>
<td>1 (33)</td>
<td></td>
</tr>
<tr>
<td>Other GN</td>
<td>4 (12)</td>
<td>6 (86)</td>
<td></td>
</tr>
<tr>
<td>Other GP</td>
<td>4 (12)</td>
<td>2 (50)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12 (100)</td>
<td>17 (50)</td>
<td></td>
</tr>
</tbody>
</table>

1999-02, 12,946 febrile pts, 285 with SBI; 1 Genoral meningitis, 2 Clostridium diphtheriae; 1 brain abscess; 1 Other coinfections.
RSV and SBI in Infants
- 3 year multi-center, prospective, cross sectional study for= 60 days
- 1248 pts – 269 (22%) with RSV
- SBI= bacteremia, meningitis, UTI, Enteritis

<table>
<thead>
<tr>
<th>Variable</th>
<th>RSV+ %</th>
<th>RSV- %</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SBI</td>
<td>7</td>
<td>12.5</td>
<td>11.4</td>
</tr>
<tr>
<td>UTI</td>
<td>5.4</td>
<td>10.1</td>
<td>9.1</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1.1</td>
<td>2.3</td>
<td>2</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Influenza and SBI
- Multicenter, prospective, cross sectional study over 3 flu seasons
- 1091, 844 tested for influenza (123+14.3%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Flu+ %</th>
<th>Flu- %</th>
<th>Overall %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SBI</td>
<td>2.5</td>
<td>13.3</td>
<td>11.7</td>
</tr>
<tr>
<td>UTI</td>
<td>2.4</td>
<td>10.8</td>
<td>9.6</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>0</td>
<td>2.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Enteritis</td>
<td>0</td>
<td>1.7</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Enterovirus and SBI
- Review of 1142 cases of children diagnosed with meningitis who underwent EV PCR
- Of 735 positive for EV from CSF:
  - NONE had bacterial co-infection
- King et. al., 2007
  - Single-site study of children <90 days old undergoing CSF eval for meningitis
  - EV PCR positive:
    - 1.54 day decreased in LOS
    - 33.7% shorter duration of antibiotic exposure

Deciding on Management
- All criteria missed diagnosis of SBI in <1 month olds

Managing the Febrile Infant
- No evidence any particular approach leads to difference in health outcomes
- Prospective study from Canada (2009)
  - Substantial variations in evaluation and management in tertiary pediatric EDs
  - Blood and urine tests ordered in the majority
  - Rates of LPs and antibiotic treatment differed between centers

Management of Infants < 1 Month of Age
- Most experts: automatic “rule-out sepsis” work-up
  - CBC with differential
  - Blood culture
  - Urine culture via straight cath
  - CSF analysis and culture (REVISE optional if low risk and off abx)
    - Glucose, protein, gram stain, cell count, and culture
  - If clinically indicated
    - CXR
    - NP sample for RSV/Influenza A screen/RVP
  - Admit
    - Empirc antibiotics until cultures negative for 24-36 hrs
Management of Infants 1-2 Months of Age

- Usual practice in ill-appearing infant
  - Blood culture, CBC with diff
  - CSF evaluation (if non-low risk)
  - Urine culture and UA
- If clinically indicated
  - CXR
  - NP sample for RSV/Influenza A screen/RVP as indicated
- Hospitalize
- Empiric antibiotics until cultures negative for 24-36 hrs

Management Options

- Partial Work-up and d/c if low risk
  - >28 days
- Full work-up w/ LP: IM Ceftriaxone - home
  - In low risk >28 days
  - Full work up with parenteral anbx
  - >28 days

Management of Low-Risk Infants 1-2 Months of Age

- Negative laboratory screen
- CBC and UA
- LP may not be necessary if no antibiotics are given
- Blood and urine cultures should be obtained
- Hospitalization without antibiotics
  - No LP for those in low risk and >28-30 days
  - No untoward effects from waiting for Cx
  - May be managed outpatient w/out antibiotics or w/ceftriaxone (50 mg/kg)
  - Must have reliable follow-up within 24 hours

Management of Infants 2-3 Months of Age

- No consensus on management
- Risk of SBI similar to older infants
- Ill-appearing
  - Full laboratory evaluation
  - Admission and empiric antibiotics
- Well-appearing
  - Likely can treat per AAP febrile UTI guidelines
  - May be managed as an outpatient off antibiotics or with single dose ceftriaxone if reliable follow-up

Antibiotic Regimen

- Infants 0-30 days
  - Ampicillin and gentamicin or cefotaxime
  - Option to use cefotaxime alone?
- Infants 31-60 days
  - Cefotaxime (or amp and gent)
  - Ampicillin in severely ill (Listeria)
- Infants >60 days
  - Ceftriaxone
  - Risk of ceftriaxone causing bilirubin displacement and theoretical risk of biliary sludging in <2 month old

Duration of Antibiotic Therapy

- Based on result of cultures or other tests and review of history and clinical response
  - Check cultures after a true minimum incubation period of 24 hours
    - Probability of identifying SBI after 24 hours is 1.1%
    - Mean time to blood culture positivity
      - true pathogens 17.5 hours
      - contaminants 27.9 hours
    - Median time to positivity
      - urine cultures 16 hours
      - CSF cultures 16 hours
Follow-up for Outpatient Treatment

- Recommended parent education prior to discharge home
  - Temperature measurement
  - When to call physician
  - Anticipated course of illness
- Arrange follow-up within 24 hours by phone or visit

Follow-up for Outpatient Treatment

- If patient received Ceftriaxone should return for 2nd dose
- Return for evaluation and hospitalization if
  - Any deterioration in clinical status or worsening of fever
  - Positive blood culture (not a contaminant)
  - Positive urine culture in infant with continued fever

The danger of doing more:

- Pingree, et. al. (2015)
- 10-year retrospective study of “low-risk” infants by Boston criteria 28-60 days old to ED with fever
- Compared “normal LP” to “Traumatic” or “unsuccessful” LP
- 929 infants, 173 (18.6%) w/ traumatic/unsuccessful LP
  - Hospitalization 72.3% vs 18.1% normal LP
  - SBI rate: 2.9% vs 4.1% (no difference)
  - None had bacterial meningitis

Can CPGs Help Standardize Practice?

- Byington, et. al. 2012, EB CPG employed through Intermountain Health
- 2004-2009, review of 8431 episodes:
  - Admit: 13% to 16%
  - Increase in completion of lab testing: CBC, UA, Bcx, Ucx
    - EV dx 25% to 36%
    - Receipt of rec abx +15%
    - Abx stopped by 36H +16%
    - Mean LOS 66-94H

Other CPGs

- Aronson, et. al., 2015
  - Survey of 33 pediatric ED
    - Asked whether had febrile infant CPG
    - Content of CPG
  - 21/33 ED had CPG
  - No variation in recs for infants ≤28 days
  - CSF testing, ceftriaxone use recs varied for infants 29-56d old
  - Variation in use of CSF testing, abx in older age group
Reducing Excessive Variation in the Infant Sepsis Evaluation (REVISE)

- 132-site practice standardization project
- Sponsored by AAP
  - Value in Inpatient Pediatrics (VIP) Network
  - Practice Improvement Network (PIN)
- Developed consensus recommendations and benchmarks for managing well-appearing febrile infants 7-59 days old
- Children’s Mercy lead in developing change package

CMPeDS: Pediatric Decision Support Mobile app released as part of change package, developed at CMH

- Mobile device-based electronic clinical decision support tool
- Part of the national practice standardization project REVISE
- Developed over 12 months
  - Updates ongoing
  - Part of change package

CMPeDS Development

- Incorporating expert consensus for content
- Interface revised with assistance of human factors expertise
- Usability analysis
- Heuristic analysis
- Google Analytics encoded to track usage patterns

Future directions

- AAP National Guidelines
  - Coming soon?
- Practice standardization efforts
- Lots of research opportunities

CMPeDS: Users as of 8/24/2017
Summary

- SBI in young infants cannot be reliably diagnosed by clinical exam alone
- Prior to availability of culture results, management must rely on a combination of physical examination findings and diagnostic screening tests
- Management is age and risk factor related