Fever in Young Infants
7 – 90 days of age

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Disclosures

I have no actual or potential conflicts in relation to this presentation.
Objectives

1. Understand the “definition” of fever in neonates and young infants

2. Discuss the diagnostic evaluation and management of febrile young infants from 7 – 90 days of age

3. Discuss how to identify infants at “low risk” of having a serious bacterial infection (SBI)

4. Understand gaps in the evidence of care for young febrile infants
Definitions

- **Neonate**: birth – 28 days old
- **Young Infant**: 29 – 90 days old
- **Fever without a source**: acute febrile illness without localizing signs or symptoms despite a careful history and physical examination
- **Occult bacteremia**: presence of bacteria in the bloodstream of a febrile child who may not appear particularly sick and has no apparent other source of infection
How is fever defined in this age group?

• Most widely accepted definition of normal body temp is 37° C or 98.6° F based on 19th century studies by Wunderlich ¹

• Core temperature shows a diurnal variation of 1° C, the nadir occurring in the early morning hours and the peak in the late afternoon

• More recent studies have shown that body temperature fluctuates from 36.6 – 37.9°C or 97.9 – 100.2°F ²,³

Birth – 90 days old: FEVER is rectal temp ≥ 38°C or 100.4°F
Does it matter how the temperature is taken?

- Rectal temperature = GOLD STANDARD

- Axillary and tympanic temperatures are not reliable in young infants

- Temporal artery temperatures are not precise enough for crucial decision making
Why evaluate all febrile young infants?

• Common for young febrile infants to have few, if any, clues to underlying illness

• Susceptible to infection due to immature immune system 
  – definable deficiencies in specific antibody, complement and phagocyte number and function
  – increased susceptibility to GBS and other pyogenic bacteria
Why evaluate all febrile young infants?

• Identify those young infants at high risk for serious bacterial illness (SBI)
  – Urinary tract infection
  – Bacteremia
  – Meningitis
  – Bacterial gastroenteritis
  – Pneumonia
  – Bone / joint infections
Evaluation of Fever

• Thorough history

• Complete undressed physical exam

• Laboratory evaluation

• Disposition depends on results above…
  – Admit for empiric antibiotics
  – Admit for observation +/- empiric antibiotics
  – Close outpatient follow-up +/- empiric antibiotics
HISTORY

• Caretaker’s report of well-being
  – Activity level: playful & smiling, consolable, irritable, lethargic
  – Hydration status: fluid intake, urine output
  – Respiratory sx: cough, work of breathing, retractions, grunting
  – GI sx: vomiting, diarrhea, abdominal pain
  – Urinary sx: dysuria, frequency, dysuria
  – ENT sx: conjunctivitis, eye discharge, sore throat, rhinorrhea
  – Skin sx: overall color, new rashes
• **Past Medical History**
  
  – *Detailed birth history*: gestational age, mode of delivery, maternal infections during pregnancy, antibiotics during pregnancy, maternal fever at time of delivery, maternal GBS status
  
  – *Immunization status*
  
  – *Underlying medical illnesses*
  
  – *Previous hospitalizations*
• **Social History**
  – *Contact with ill persons*
  – *Day care attendance*
  – *Young, school-age siblings*
  – *Recent travel*
Physical Exam

• Vital Signs, including Pulse Oximetry

• General Appearance

• Complete UNDRESSED physical exam
“Toxic” or ill-appearing children

• “Toxic” Signs / Symptoms
  – Unable to console
  – Lethargy
  – Poor perfusion
  – Capillary refill > 2 sec
  – Cyanosis
  – Tachypnea (RR > 60)
  – Hypothermia (temp ≤ 36°C or 96.8°F)

• Admit to hospital for full sepsis work-up (blood, urine, CSF cultures)

• Empiric broad-spectrum antibiotics
How good is a H&P at identifying serious infections in febrile young infants?

After a history and physical examination…

the source of fever remains inapparent in 20% of children < 3 months of life.
Prevalence of bacteremia, bacterial meningitis, and urinary tract infection (UTI) in febrile infants

Rate of bacteremia and meningitis in febrile young infants appear to decrease with age. 

<table>
<thead>
<tr>
<th>Age</th>
<th>Bacteremia</th>
<th>Bacterial Meningitis</th>
<th>UTI + bacteremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 1 mo</td>
<td>3%</td>
<td>1.2%</td>
<td>17%</td>
</tr>
<tr>
<td>1 – 2 mo</td>
<td>1.5%</td>
<td>0.4%</td>
<td>8%</td>
</tr>
<tr>
<td>2 – 3 mo</td>
<td>0.7%</td>
<td>0%</td>
<td>6%</td>
</tr>
</tbody>
</table>

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Decision Rules for Assessment of Fever in Young Infants

- 3 most commonly applied outpatient criteria
  - Rochester Criteria
  - Philadelphia Protocol
  - Boston Criteria

- Difficult to compare because different inclusion criteria, lab testing and clinical implications for decision making

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## Decision Rules for Assessment of Fever in Young Infants

<table>
<thead>
<tr>
<th></th>
<th>ROCHESTER</th>
<th>PHILADELPHIA</th>
<th>BOSTON</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever</strong></td>
<td>Temp ≥ 38°C (100.4°F)</td>
<td>Temp ≥ 38.2°C (100.8°F)</td>
<td>Temp ≥ 38°C (100.4°F)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>≤ 60 days</td>
<td>29 – 56 days</td>
<td>28 – 89 days</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>- Term (&gt;37 weeks)</td>
<td>- No immune deficiency</td>
<td>- No antibiotics</td>
</tr>
<tr>
<td></td>
<td>- No antibiotics</td>
<td></td>
<td>- No antibiotics</td>
</tr>
<tr>
<td></td>
<td>- Never hospitalized</td>
<td></td>
<td>- No immunizations in past 48 hours</td>
</tr>
<tr>
<td></td>
<td>- No unexplained hyperbilirubinemia</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>- No chronic illness</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>- Not hospitalized longer than mother</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CBC with diff</strong></td>
<td>WBC of 5000 – 15,000 Abs Bands ≤ 1500</td>
<td>WBC ≤ 15,000 Band:Neutrophil ratio of &lt; 0.2</td>
<td>WBC ≤ 20,000</td>
</tr>
<tr>
<td><strong>Urinalysis</strong></td>
<td>WBC ≤ 10 / hpf</td>
<td>WBC ≤ 10 / hpf</td>
<td>WBC ≤ 10 / hpf</td>
</tr>
<tr>
<td><strong>Stool</strong></td>
<td>WBC ≤ 5 / hpf</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td><strong>LP</strong></td>
<td>None</td>
<td>WBC ≤ 8 / hpf</td>
<td>WBC ≤ 10 / hpf negative Gram stain</td>
</tr>
<tr>
<td><strong>CXR</strong></td>
<td>-----</td>
<td>Negative</td>
<td>Negative if obtained</td>
</tr>
</tbody>
</table>
Febrile Neonate (≤ 28 day old)

• Detailed history

• Complete undressed physical exam

• Full sepsis evaluation
  – CBC with differential
  – Blood culture
  – Urinalysis / micro + Urine culture
  – Lumbar puncture for CSF analysis + culture
  – Consider HSV evaluation

• Empiric antibiotics
  – Ampicillin + Gentamicin
  – Ampicillin + Cefotaxime
What about fever in 29 – 90 day old?

• Controversy and variation exist regarding the evaluation and management in this population

• Many have self-limited viral infections

• Routine hospitalization and administration of IV antibiotics is costly and associated with iatrogenic complications
What about fever in 29 – 90 day old?

• Prospective research has resulted in criteria to help distinguish patients at “low risk” for bacterial disease from patients at “high risk”

• Help identify which patients should be hospitalized and which patients can be treated as outpatients either with or without antibiotics
“Low Risk” Clinical Criteria

• Previously healthy, term infant with uncomplicated nursery stay

• Non-toxic clinical appearance

• No evidence of skin / soft tissue, bone / joint or ear infections on exam

• No prior antibiotic treatment
## “Low Risk” Laboratory Criteria

| CBC with diff | WBC count | 5,000 – 15,000  
Absolute Bands | <1,500 |
|----------------|-----------|----------------|
| **Urinalysis** | Clear   | Negative nitrites & leukocyte esterase  
WBC ≤ 5 / hpf |
| (from catheterized sample or suprapubic aspirate) | | |
| **CSF** | 0-28 days of age  
WBC cell count: 0-22 / mm³ |  |
| > 29 days days of age  
WBC cell count: 0-7 / mm³ | Normal protein |
| **If diarrhea present...** | Stool with < 5 WBCs / hpf |
| **If respiratory symptoms...** | normal CXR |
What does “Low Risk” mean?

• Neonates
  ▪ Boston & Philadelphia criteria have been applied retrospectively to infants in the first month of life
  ▪ 3% of the infants who fulfilled ALL the low-risk criteria were found to have an SBI

As neonates have the highest risk of SBI and most limited range of signs/symptoms, this suggests that all infants ≤ 28 days be hospitalized for complete sepsis evaluation.

• Young Infants
  ▪ In 29 – 90 day old infants, fulfilling ALL the low-risk criteria has been shown to have a NPV >98% for any SBI and >99% for bacteremia
Let’s put these into practice

Recommended Management Strategies

**Age**
- Neonate 0 – 28 days old
- OR toxic-appearing infant of any age
- with rectal temp ≥ 38°C or 100.4°F

**Age**
- Young Infant 29 – 60 days old
  - with rectal temp ≥ 38°C or 100.4°F

**Age**
- Young Infant 61 – 90 days old
  - with rectal temp ≥ 38°C or 100.4°F
# Recommended Management

<table>
<thead>
<tr>
<th>Age</th>
<th>Evaluation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate 0 – 28 days old&lt;br&gt;OR toxic-appearing infant of any age with rectal temp ≥ 38°C or 100.4°F</td>
<td>1. Thorough history&lt;br&gt;2. Complete undressed physical exam&lt;br&gt;3. Laboratory Evaluation&lt;br&gt;  ▪ CBC with differential&lt;br&gt;  ▪ Blood culture&lt;br&gt;  ▪ Urine via cath or suprapubic aspirate for urinalysis / micro and urine culture&lt;br&gt;  ▪ Lumbar puncture for CSF: cell count, protein, glucose, Gram stain, aerobic culture&lt;br&gt;  ▪ Consider HSV and enterovirus PCR for CSF&lt;br&gt;  If diarrhea: stool micro &amp; culture&lt;br&gt;  If respiratory symptoms: CXR</td>
<td>1. Admit to hospital for IV/IM antibiotics until culture results available:&lt;br&gt;  ▪ Ampicillin + Gentamicin or&lt;br&gt;  ▪ Ampicillin + Cefotaxime&lt;br&gt;  * If concern for HSV, then add Acyclovir&lt;br&gt;  * If evidence of skin &amp; soft tissue infection, then substitute Vancomycin for Ampicillin</td>
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### Recommended Management

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</table>
| Young Infant 29 – 60 days old with rectal temp ≥ 38°C or 100.4°F | 1. Thorough history  
2. Complete undressed physical exam  
3. Laboratory Evaluation  
   ▪ Same as for neonate  
4. Determine if patient is “Low Risk” for SBI by meeting ALL criteria:  
   ▪ No known immunodeficiency  
   ▪ Non-toxic appearance  
   ▪ No evidence of skin, soft tissue, bone, joint or ear infection on exam  
   ▪ WBC between 5,000 - 15,000  
   ▪ Band:Neutrophil ratio <0.2  
   ▪ Normal urinalysis  
   ▪ Normal CSF parameters  
   ▪ Normal CXR (if done) | 1. If high risk or toxic-appearing, admit to hospital for IV/IM antibiotics until culture results available:  
   ▪ Ampicillin + Gentamicin or  
   ▪ Ampicillin + Cefotaxime  
   * If concern for HSV, then add Acyclovir  
   * If evidence of skin & soft tissue infection, then substitute Vancomycin for Ampicillin  
2. If low-risk, choose one of following options:  
   a) Administer Ceftriaxone 50 mg/kg IM, re-examine at 24 and 48 hours. **MUST perform LP** prior to antibiotics.  
   b) Consider admitting to hospital for observation. No antibiotics and re-examine at 24 and 48 hours. May consider deferring LP.
## Recommended Management

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<th>Evaluation</th>
<th>Management</th>
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</thead>
<tbody>
<tr>
<td>Young Infant 61 – 90 days old</td>
<td>1. Thorough history</td>
<td>1. If high-risk or toxic-appearing, then perform LP and admit to hospital for IV/IM antibiotics until culture results available:</td>
</tr>
<tr>
<td></td>
<td>2. Complete undressed physical exam</td>
<td>- Ceftriaxone monotherapy</td>
</tr>
<tr>
<td></td>
<td>3. Laboratory Evaluation</td>
<td>* If concern for HSV, then add Acyclovir</td>
</tr>
<tr>
<td></td>
<td>- CBC with differential</td>
<td>* If CSF parameters concerning for meningitis or evidence of skin &amp; soft tissue infection, then add Vancomycin</td>
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<td></td>
<td>- Blood culture</td>
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<td></td>
<td>- Urine via cath or suprapubic aspirate for urinalysis / micro and urine culture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>** LP if clinical concern for meningitis</td>
<td></td>
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<tr>
<td></td>
<td>If diarrhea: stool micro &amp; culture</td>
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<td></td>
<td>If respiratory symptoms: CXR</td>
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When to worry about HSV?

<table>
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<th>HSV Risk Factors</th>
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<tbody>
<tr>
<td>Maternal primary HSV infection</td>
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<tr>
<td>Maternal fever</td>
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<td>Vaginal delivery</td>
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<tr>
<td>Prematurity</td>
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<td>Neonatal seizures</td>
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<tr>
<td>Vesicular rash</td>
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<tr>
<td>CSF pleocytosis</td>
<td></td>
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<tr>
<td>Elevated hepatic enzymes</td>
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Initial signs can occur anywhere between birth – 6 weeks of age

3 manifestations of HSV
- 45% skin, eye, mucous membrane (SEM)
- 33% CNS
- 25% disseminated (liver, lungs)

Consider in neonates with the following:
- sepsis syndrome (including hypothermia)
- negative bacterial culture results
- severe liver dysfunction
- consumptive coagulopathy

Can be neurologically devastating or fatal if not treated in early stages of disease
If you did suspect HSV...

Evaluation

• CSF for HSV PCR (priority)
• Blood for HSV PCR
• “Surface cultures” consisting of conjunctiva, nasopharyngeal & rectal HSV culture (or PCR)
• AST / ALT

Treatment

• Acyclovir 20 mg/kg IV every 8 hours
What to do when the parents report a fever at home and then patient is afebrile in your office?

Retrospective study of 292 infants <2 months of age who received an evaluation and were admitted to the hospital. 92% of the infants who had rectal temperature at home had subsequent fever in next 48 hours. ¹³
The Tactile Fever

What to do when the parents report a tactile fever at home and then patient is afebrile in your office?

None of the infants with tactile temperature at home who were afebrile on presentation had fever in subsequent 48 hours. 

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Febrile young infants with RSV bronchiolitis or influenza still have a “clinically significant risk” of UTI (~2-5%) $^{14,15}$

**Recommendation**
Urinalysis + micro and urine culture should be performed at time of diagnosis or if febrile for >72 hours.
Among febrile infants, prevalence of SBI is less in the initial 24 hours after immunizations. However, there is still ~3% risk of UTI. 16

**Recommendation**
- Urinalysis + micro and urine culture should be performed in febrile infants who present within 24 hours of immunization.

Infants who present greater than 24 hours after immunizations with fever should be managed similarly to infants who have not received routine immunizations.


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