Evaluating Fever in Infants

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Disclosures

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

I will be discussing a current national QI project related to evaluation of febrile infants.
Objectives

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

2. Discuss the diagnostic evaluation and management of febrile infants of varying ages
   - 7 – 28 days of age
   - 29 – 60 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 febrile infants
Definitions

• *Neonate*: birth – 28 days old

• *Infant*: birth – 1 year of age

• *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
How is fever defined in infants?

- Assessment protocols used in ED departments and urgent care centers have lead to various definitions:
  - $\geq 38.0 \, ^\circ\text{C} = 100.4 \, ^\circ\text{F}$
  - $\geq 38.5 \, ^\circ\text{C} = 101.3 \, ^\circ\text{F}$
  - $\geq 39 \, ^\circ\text{C} = 102.2 \, ^\circ\text{F}$

- Depends on patient age and reference source

  Birth – 60 days old: FEVER is rectal temp $\geq 38^\circ\text{C}$ or 100.4°F
  > 2 months old: FEVER is more variably defined

Many define fever as documented temp $\geq 38^\circ\text{C}$ or 100.4°F regardless of age
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
The mammalian thermoregulatory system remains a bit of a mystery – TNF-α, IL-6 and IL-1Aβ are major contributors – Drive production of prostaglandin E in COX-2 and STAT3 metabolic pathways

Fever is major host defense mechanism that has evolved and been conserved over time – Studies of ICU pts support the important role of fever in protecting host against microbial invasion
• Febrile child can be highly stressful for the family (and occasionally the clinician)

• Common belief that fever is a disease rather than a symptoms or sign of illness

• Requires education regarding…
  – Beneficial effect of fever on immune system
  – Homeostatic process so body does not allow fever to rise out of control to potentially lethal levels (exceedingly rare to exceed 107 °F)

“Fever is the body’s natural and normal response to something that stimulates the body’s immune system. In children, fever is most commonly caused by self-limited viral infections.”
Why evaluate all young febrile infants?

• Common for young febrile infants (< 3 months of age) to have few, if any, clues to underlying illness

• Susceptible to infection due to immature immune system 6
  – definable deficiencies in specific antibody, complement and phagocyte number and function
  – increased susceptibility to GBS and other pyogenic bacteria
Why evaluate all young febrile 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
• Caretaker’s report of well-being
  – Activity level: playful & smiling, consolable, irritable, lethargic
  – Hydration status: fluid intake, urine output
  – Respiratory sxs: cough, work of breathing, retractions, grunting
  – GI sxs: vomiting, diarrhea, abdominal pain
  – Urinary sxs: dysuria, frequency, dysuria
  – ENT sxs: conjunctivitis, eye discharge, sore throat, rhinorrhea
  – Skin sxs: 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>
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 \(^9\)
### 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 $\geq 38 , ^\circ C$</td>
<td>Temp $\geq 38.2 , ^\circ C$</td>
<td>Temp $\geq 38 , ^\circ C$</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>$\leq 60$ 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 immunizations in past 48 hours</td>
</tr>
<tr>
<td></td>
<td>- Never hospitalized</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- No unexplained hyperbilirubinemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- No chronic illness</td>
<td></td>
<td></td>
</tr>
<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 $\leq 1500$</td>
<td>WBC $\leq 15,000$</td>
<td>WBC $\leq 20,000$</td>
</tr>
<tr>
<td><strong>Urinalysis</strong></td>
<td>WBC $\leq 10$ / hpf</td>
<td>WBC $\leq 10$ / hpf</td>
<td>WBC $\leq 10$ / hpf</td>
</tr>
<tr>
<td><strong>Stool</strong></td>
<td>WBC $\leq 5$ / hpf</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td><strong>LP</strong></td>
<td>None</td>
<td>WBC $\leq 8$ / hpf</td>
<td>WBC $\leq 10$ / hpf</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WBC $\leq 10$ / hpf negative Gram stain</td>
<td></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
  - Meningitis / encephalitis panel (if available)
  - 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

<table>
<thead>
<tr>
<th>Test</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| 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 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

<table>
<thead>
<tr>
<th>Age</th>
<th>Neonate 0 – 28 days old OR toxic-appearing infant of any age with rectal temp ≥ 38°C or 100.4°F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Young Infant 29 – 60 days old with rectal temp ≥ 38°C or 100.4°F</td>
</tr>
<tr>
<td>Age</td>
<td>Young Infant 61 – 90 days old with rectal temp ≥ 38°C or 100.4°F</td>
</tr>
</tbody>
</table>
# Recommended Management

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

## Evaluation
1. Thorough history
2. Complete undressed physical exam
3. Laboratory Evaluation
   - CBC with differential
   - Blood culture
   - Urine via cath or suprapubic aspirate for urinalysis / micro and urine culture
   - Lumbar puncture for CSF: cell count, protein, glucose, Gram stain, aerobic culture
   - Consider HSV and enterovirus PCR for CSF

## Management
1. 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

If diarrhea: stool micro & culture
If respiratory symptoms: CXR
Recommended Management

<table>
<thead>
<tr>
<th>Age</th>
<th>Evaluation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young Infant 29 – 60 days old with rectal temp $\geq 38^\circ\text{C}$ or $100.4^\circ\text{F}$</td>
<td>1. Thorough history&lt;br&gt;2. Complete undressed physical exam&lt;br&gt;3. Laboratory Evaluation&lt;br&gt;</td>
<td>1. If high risk or toxic-appearing, then perform LP and admit to hospital for IV/IM antibiotics until culture results available:&lt;br&gt;</td>
</tr>
<tr>
<td></td>
<td>Same as for neonate&lt;br&gt;&lt;br&gt;4. Determine if patient is “Low Risk” for SBI by meeting ALL criteria:</td>
<td>▪ Ampicillin + Gentamicin OR&lt;br&gt;▪ Ampicillin + Cefotaxime&lt;br&gt;&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>
</tr>
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</table>
### Recommended Management

<table>
<thead>
<tr>
<th>Age</th>
<th>Evaluation</th>
</tr>
</thead>
</table>
| Young Infant 61 – 90 days old | 1. Thorough history  
2. Complete undressed physical exam  
3. Laboratory Evaluation  
   ▪ CBC with differential  
   ▪ Blood culture  
   ▪ Urine via cath or suprapubic aspirate for urinalysis / micro and urine culture  
   ** LP if clinical concern for meningitis  
If diarrhea: stool micro & culture  
If respiratory symptoms: CXR |

<table>
<thead>
<tr>
<th>Management</th>
</tr>
</thead>
</table>
| 1. If high-risk or toxic-appearing, then perform LP and admit to hospital for IV/IM antibiotics until culture results available:  
  ▪ Ceftriaxone monotherapy  
  * If concern for HSV, then add Acyclovir  
  * If CSF parameters concerning for meningitis or evidence of skin & soft tissue infection, then add Vancomycin |
| 2. If low-risk:  
a) No antibiotics and re-examine at 24 and 48 hours. |
When to worry about HSV?

### HSV Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal hx of HSV infection</td>
</tr>
<tr>
<td>Maternal fever</td>
</tr>
<tr>
<td>Vaginal delivery</td>
</tr>
<tr>
<td>Prematurity</td>
</tr>
<tr>
<td><strong>Neonatal seizures</strong></td>
</tr>
<tr>
<td><strong>Vesicular rash</strong></td>
</tr>
<tr>
<td><strong>CSF pleocytosis</strong></td>
</tr>
<tr>
<td><strong>Elevated hepatic enzymes</strong></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>

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
The Vanishing Fever

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
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. ¹³
Risk of SBI with RSV or Influenza

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.  

**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.
<table>
<thead>
<tr>
<th>Age</th>
<th>Evaluation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant &gt; 90 days – 1 year with rectal temp ≥ 38°C or 100.4°F</td>
<td>1. Thorough history</td>
<td>1. If toxic-appearing, then complete sepsis evaluation (including 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 CSF parameters concerning for meningitis or evidence of skin &amp; soft tissue infection, then add Vancomycin</td>
</tr>
<tr>
<td></td>
<td>▪ Bagged UA/micro to screen for UTI. If “dirty” then needs urine via cath or suprapubic aspirate for UA/micro and urine culture.</td>
<td>2. If well-appearing, no source of infection on exam and labs are normal:</td>
</tr>
<tr>
<td></td>
<td>▪ If respiratory symptoms: consider respiratory viral testing if it changes management</td>
<td>▪ Re-evaluate in 24 – 72 hours</td>
</tr>
<tr>
<td></td>
<td>▪ If diarrhea: stool micro &amp; culture</td>
<td>▪ Expand work-up if patient remains febrile for ≥ 1 week</td>
</tr>
<tr>
<td></td>
<td>▪ Consider CBC with diff, CRP and +/- blood culture</td>
<td></td>
</tr>
</tbody>
</table>
NEW: Project REVISE

- REVISE = Reducing Excessive Variability in Infant Sepsis Evaluations

- Value in Inpatient Pediatrics (VIP) Network
  - Established a national QI collaborative to improve and standardize care for febrile infants between ages 7 - 60 days
  
  - Specific Aims
    1. Decrease admissions for infants presenting to ED’s with fever who are at low risk of bacterial infection
    2. Decrease variation in care of febrile infants presenting to the ED and/or hospital
    3. Decrease LOS for infants admitted to the hospital with fever
    4. Decrease use of unnecessary chest x-rays in the care of febrile infants
NEW:  Project REVISE

• **Clinical Practice Guidelines for Febrile Infants**
  – Internal guideline created in 2017
  – Reflects UIHC involvement with Project REVISE

See attached PDF
Bibliography

Objective:
Significant variation exists in the approach to the febrile infant both within the University of Iowa Stead Family Children’s Hospital (SFCH) and throughout the nation. The purpose of this Febrile Infant Clinical Practice Guideline is to standardize care of this patient population with the goal of improving patient outcomes. There is currently no standard of care of febrile infants at University of Iowa Hospital Stead Family Children’s Hospital. This leads to inconsistent care and can be a source of confusion for patients and families.

This guideline should apply to most of the population, however, will not encompass all scenarios. Clinical decision making by the individual physician at the bedside is an important part of any guideline.

Attention should be drawn to the further age stratification of these guidelines. Two separate algorithms exist, 1). 7 to 28 days of life (page 9) and 2). 29 to 60 days of life (page 10)

Definition:
Fever in infants 7 to 60 days of life is elevation of central temperature to 38°C or higher.

Target Users:
Clinicians and nurses in the UIHC emergency department, Quickcare, UIHC clinic, and SFCH floors.

Guideline Inclusion Criteria:
This guideline is to direct care for infants 7 to 60 days of age who present with a temperature of greater than or equal to 38.0°C by any route by either healthcare worker or parental report or taken in the ED/Quickcare/UIHC clinic/inpatient setting.

Infants with gestational age less than 37 weeks, with congenital medical and/or surgical co-morbidities, and those are hospitalized at any time since birth are high risk for bacterial infections and are included in this guideline.

Guideline Exclusion Criteria:
Infants <7 days or >60 days of age, or any infant without a fever either on exam or by history.

Clinical Questions Answered by this Guideline:
1. What criteria can be used to determine if a febrile infant 7-60 days of age is at low risk for a bacterial infection?
2. When should HSV testing be performed and treatment initiated in a febrile infant 7 to 60 days of age?

**Differential Diagnosis:**
The main differential is a bacterial infection that can manifest as an urinary tract infection, bacteremia, meningitis, pneumonia and/or bacterial gastroenteritis. Viral illnesses can also cause fever in infants.

**Practice Recommendations:**
- **Assessing fever in infant**

**History:** Fever in infants 7 to 60 days should not be ignored. Parental report of fever, regardless of the temperature measurement technique used, is to be believed and the infant should be evaluated further. (Callanan 2003). There is mixed evidence as to whether the clinician should rely on the ability of a parent to detect a fever in the infant population without a thermometer. Whether the clinician accepts the report as sole evidence of fever is an individual decision. (Teng, Ng et al. 2008; Katz-Sidlow, Rowberry et al. 2009)

**Management of Ill Appearing Febrile Infants 7 to 60 Days**

**Full Sepsis Evaluation of Ill Appearing Infants**

A full sepsis evaluation is recommended for all ill appearing febrile infants. Ill appearing is further defined as

1. Clinical presentation characterized by lethargy, evidence of poor perfusion, cyanosis, hypoventilation or hyperventilation
2. Significant abnormalities in vital signs

A full sepsis evaluation includes the following:

1. Stat glucose
2. Urinalysis (UA), urine microscopy, and urine culture via catheter
3. Complete blood count (CBC) with differential
4. Blood culture
5. Complete metabolic panel (CMP)
6. CRP
7. Cerebral spinal fluid (CSF) cell count with differential, protein, and glucose
8. CSF meningitis/encephalitis panel (includes gram stain and bacterial culture)
9. If respiratory symptoms (cough, rhinorrhea), obtain a respiratory viral panel (RVP); consider a 2 view of the chest *only if tachypnea for age, hypoxemia, or focal findings on exam. *In absence of respiratory signs, febrile infants are unlikely to have an abnormal chest xray. (Crain, EF et al. 1991; Bramison, RT et al. 1993; Mintegi, S et al. 2010; Hernandez, DA and Nguygen, T 2011; Baraff, LJ 2013)

These infants should undergo a Herpes Simplex Virus (HSV) Risk Assessment with the HSV Checklist (discussed later on page 6) and managed accordingly.
Inpatient Management
- All ill appearing infants are to be admitted to the hospital
- Empiric administration of IV antibiotics (+/- acyclovir depending on HSV risk) is required. Initial doses are below. For continuous therapy, please see individual drug orders.

<table>
<thead>
<tr>
<th>Age</th>
<th>Suggested Empiric First Dose</th>
<th>High risk for HSV</th>
</tr>
</thead>
</table>
| Infants 7-28 days | 1. Ampicillin 50 mg/kg IV  
                         2. Cefotaxime* 50 mg/kg IV OR Gentamicin 4 mg/kg IV | Acyclovir 20 mg/kg IV |
| Infants 29-60 days | 1. Ampicillin 50 mg/kg IV  
                         2. Cefotaxime* 50 mg/kg IV OR Ceftriaxone 100 mg/kg IV | (* may substitute cefepime 50 mg/kg IV if cefotaxime shortage) |

- Antipyretic administration: Acetaminophen may be administered (10-15 mg/kg/dose every 4-6 hours [Max 75 mg/kg/day]) PO or PR for infants with fever when assessed to be uncomfortable.
- Treatment of an infant with a positive blood, urine, or CSF culture is dependent on the infection site and the pathogen identified.

Management of Well Appearing Febrile Infants 7 to 60 Days
Identification of infants at risk for bacterial infections: The Bacterial Risk Assessment
The Bacterial Risk Assessment is based on the Rochester Criteria to further stratify which infants are at high risk for a bacterial cause of their fever. This assessment uses both the patient’s history as well as some laboratory values taken at the time of evaluation to stratify risk.

All infants evaluated for fever should have the following initial screening tests:
1. UA, urine microscopy, and urine culture via catheter
2. CBC with differential
3. Blood culture
4. CRP
5. CMP
6. If respiratory symptoms (cough, rhinorrhea), obtain a respiratory viral panel (RVP); consider a 2 view of the chest only if tachypnea for age, hypoxemia, or focal findings on exam

Infants with gestation age less than 37 weeks, with congenital medical and/or surgical co-morbidities, those hospitalized at any anytime since birth, those who had received antibiotics at any time prior to the time of evaluation including newborn hospitalization, and those with unexplained hyperbilirubinemia are high risk for a bacterial illness (low risk criteria do not apply).
Low Risk Febrile Infant

Febrile infants can be classified as low risk if they meet all the following criteria. The low risk classification equates to a 98.9% negative predictive value for having a bacterial infection. (Jaskiewicz, J et al. 1994).

- Well appearing term (greater than or equal to 37 weeks gestation) infant
- Previously healthy with no previous antibiotic use
- WBC between 5,000/mL and 15,000/mL
- UA with less than 5 WBC/hpf, that is negative for nitrites, and leukocyte esterase
- Band neutrophils <1,500/mL
- CRP <1 mg/dL

Low risk infants should not have risk factors present that would make them at risk for Herpes Simplex Virus. If any risk factor is present, infants are to be managed as high risk febrile infants (low risk criteria do not apply). Please see the Herpes Simplex Virus (HSV) Risk Assessment with the HSV Checklist (discussed later on page 6). *To note, CSF pleocytosis will not be known in this patient population unless an lumbar puncture was obtained prior to patient risk stratification. Please see management below.

Management of Low Risk Febrile Infants 7 to 28 Days

Infants determined to be low risk that are 7 to 28 days of age should be admitted to the hospital for observation without administration of antibiotics until culture results can be assessed (at minimum 24 hours).

- Blood and urine cultures are assessed until final results are available. Any positive cultures judged not to be a contaminant at any time requires the infant to undergo a lumbar puncture and antibiotic administration.
- Low risk patients eligible for discharge after 24 hours if remains well appearing and blood and urine cultures remain negative. To note, urine culture is only evaluated once per day by laboratory protocol. Urine culture results should be verified prior to discharge.

- If there is a clinical decision to administer antibiotics in this patient population, a lumbar puncture should be performed. If performing a lumbar puncture the following should be obtained.
  1. Cerebral spinal fluid (CSF) cell count with differential, protein, and glucose (Obtain concurrent serum glucose if not recently obtained).
  2. CSF meningitis/encephalitis panel (includes gram stain and bacterial culture)
- These infants should undergo a Herpes Simplex Virus (HSV) Risk Assessment with the HSV Checklist (discussed later on page 6).
- Empiric administration of IV antibiotics (+/- acyclovir depending on HSV risk) is required. Initial doses are below. For continuous therapy, please see individual drug orders.
<table>
<thead>
<tr>
<th>Age</th>
<th>Suggested Empiric First Dose</th>
<th>High risk for HSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 7-28 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Ampicillin 50 mg/kg IV</td>
<td>2. Cefotaxime* 50 mg/kg IV OR Gentamicin 4 mg/kg IV (* may substitute cefepime 50 mg/kg IV if cefotaxime shortage)</td>
<td>Acyclovir 20 mg/kg IV</td>
</tr>
</tbody>
</table>

- Antipyretic administration: Acetaminophen may be administered (10-15 mg/kg/dose every 4-6 hours [Max 75 mg/kg/day]) PO or PR for infants with fever when assessed to be uncomfortable.
- Treatment of an infant with a positive blood, urine, or CSF culture is dependent on the infection site and the pathogen identified.

**Management of Low Risk Febrile Infants 29 to 60 Days**

Infants at low risk for bacterial infection in this age group may be considered *candidates for care at home* depending on caregivers’ ability and follow up is assessed and judged to be reliable. This is determined by the Ambulatory Discharge Disposition Checklist.
- Blood and urine cultures are assessed until final results are available. Any positive cultures judged not to be a contaminant at any time requires the infant to be cared for in the hospital.
- Alternatively, the infant can be admitted to the hospital for *observation without administration of antibiotics* until culture results can be assessed (at minimum 24 hours)
- Low risk patients who were admitted are eligible for discharge at 24 hours if remains well appearing and blood and urine cultures remain negative. To note, urine culture is only evaluated once per day by laboratory protocol. Urine culture results should be verified prior to discharge.
- If there is a *clinical decision to administer antibiotics* in this patient population, a lumbar puncture should be performed. Administration of antibiotics requires hospital admission. If performing a lumbar puncture the following should be obtained.
  1. Cerebral spinal fluid (CSF) cell count with differential, protein, and glucose (Obtain concurrent serum glucose if not recently obtained).
  2. CSF meningitis/encephalitis panel (includes gram stain and bacterial culture)
- These infants should undergo a Herpes Simplex Virus (HSV) Risk Assessment with the HSV Checklist (discussed later on page 6).
- Empiric administration of IV antibiotics (+/- acyclovir depending on HSV risk) is required. Initial doses are below. For continuous therapy, please see individual drug orders.

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<td>Infants 29-60 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Ampicillin 50 mg/kg IV</td>
<td>2. Cefotaxime* 50 mg/kg IV OR Ceftriaxone 100 mg/kg IV (* may substitute cefepime 50 mg/kg IV if cefotaxime shortage)</td>
<td>Acyclovir 20 mg/kg IV</td>
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- Antipyretic administration: Acetaminophen may be administered (10-15 mg/kg/dose every 4-6 hours [Max 75 mg/kg/day]) PO or PR for infants with fever when assessed to be uncomfortable.
- Treatment of an infant with a positive blood, urine, or CSF culture is dependent on the infection site and the pathogen identified.

**Management of High Risk Infants 7-60 days**
- A lumbar puncture should be performed for all high risk infants. If performing a lumbar puncture the following should be obtained.
  1. Cerebral spinal fluid (CSF) cell count with differential, protein, and glucose
     (Obtain concurrent serum glucose if not recently obtained).
  2. CSF meningitis/encephalitis panel (includes gram stain and bacterial culture)
- These infants require hospital admission.
- These infants should undergo a Herpes Simplex Virus (HSV) Risk Assessment (discussed later on page 6).
- Empiric administration of IV antibiotics (+/- acyclovir depending on HSV risk) is required. Initial doses are below. For continuous therapy, please see individual drug orders.

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<td></td>
<td>(* may substitute ceftazidime 50 mg/kg IV if cefotaxime shortage)</td>
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- Antipyretic administration: Acetaminophen may be administered (10-15 mg/kg/dose every 4-6 hours [Max 75 mg/kg/day]) PO or PR for infants with fever when assessed to be uncomfortable.
- Treatment of an infant with a positive blood, urine, or CSF culture is dependent on the infection site and the pathogen identified.
- Patient would be eligible for discharge at 36 hours if remains well appearing and blood, urine, CSF cultures, and HSV PCRs (if sent) remain negative. To note, urine culture is only evaluated once per day by laboratory protocol. Urine culture results should be verified prior to discharge.

**Identification of Infants at Risk for Herpes Simplex Virus (HSV) Infection:**

**HSV Checklist**

**Epidemiology**
1. The prevalence of HSV infection is low: 0.3% in neonates with fever and 1.0% in neonates with fever and CSF pleocytosis (Caviness, Demmler et al. 2008) or 5.1 cases per 100,000 live births (Mahnert, Roberts et al. 2007).
2. Mortality and morbidity for untreated neonatal HSV disease is high.
3. HSV can manifest as (RedBook 2015)
a. Disease localized to the skin, eye, and/or mouth (SEM disease): 45% of cases
b. Localized CNS disease, with or without skin involvement (CNS disease): 30% of cases
c. Disseminated disease involving multiple organs, most prominently liver and lungs (also present in 60% to 75% of cases also involving the CNS): 25% of cases

**HSV Risk Factors**

Infants 7 to 60 days of life are recommended for HSV testing if they present with any of the following:
- Maternal history of HSV (prior disease or active lesions)
- History of seizures or seizures during presentation
- Vesicles on skin exam (including scalp)
- CSF with pleocytosis for age (>12/μL in 7-28 days of age; >6/μL in 29-60 days of age [90th percentile per Harriet Lane])
- Elevated ALT (>25 U/L in 7-28 days of age; >35 U/L in males or >30 U/L in females in 29-60 days of age)
- Elevated AST (>50 U/L)
- Thrombocytopenia (<150,000/μL)

**Diagnostic Testing for HSV High Risk Infants**

The following diagnostic tests are recommended *in addition* to the full diagnostic work up for febrile infants as described above:
- Verification that the CSF meningitis/encephalitis panel has been sent (includes HSV CSF PCR)
- HSV surface (mouth, nasopharynx, conjunctivae, rectum) and vesicle swabs for PCR
- HSV blood PCR

**Inpatient Management for High Risk HSV Infants**

1. These infants require hospital admission.
2. Empiric administration of IV antibiotics as discussed above is required.
3. Empiric treatment of suspected HSV infection is required: starting dose of acyclovir 20 mg/kg/dose IV. For continuous therapy, please see individual drug orders.
4. Treatment duration is determined by the clinical manifestation.
5. Patient would be eligible for discharge if remains well appearing and blood, urine, CSF cultures and HSV PCRs remain negative. To note, urine culture is only evaluated once per day by laboratory protocol. Urine culture results should be verified prior to discharge.

**Guideline Preparation:**

This project was developed by an expert group comprised of emergency and inpatient physicians with expertise and interest in febrile infant management as part of the Reducing Excessive Variability in the Infant Sepsis Evaluation Project (also known as
Project REVISE). The lead authors of the AAP clinical practice guideline on fever in infants under 3 months – that is currently under development – served as advisors to ensure that the metrics for this project would not conflict with and would be slightly more conservative than the potential final guideline recommendations. The University of Iowa Stead Family Children’s Hospital serves as one of the teams in a 133-team international QI collaborative designed to improve and standardize care for febrile infants between the ages of 7 to 60 days.

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**References**