Fever Without a Source
Clinical Guideline

October 25, 2017
Definition

For the purpose of this pathway, Fever Without a Source (FWS) is defined as an acute febrile illness with temperature of 38°C (100.4°F) or greater taken rectally and no identifiable source of infection following a thorough history and physical examination in patients under 6 months of age. Patients with serious and/or life-threatening infection, especially young infants, may present with hypothermia (below 36°C or 96.8°F) and may be treated using this pathway. Approximately 12% of infants under 30 days of age and 9% of infants 30-90 days of age will have a serious bacterial infection (SBI), such as bacteremia, meningitis, or urinary tract infection (UTI). Because the clinical exam alone is unable to reliably predict serious bacterial illness in young infants, providers must rely on a combination of history, exam, diagnostic tests, and risk factors to reduce morbidity and mortality in this patient population.

Epidemiology

The most common cause of fever without localizing signs is a viral infection. The key point of evaluation is distinguishing which young infants have a serious bacterial infection and using a standardized assessment to stratify risks for these infections in young infants.

Most studies used to stratify risk for serious bacterial infection in neonates have defined a fever as a rectal temperature of 38 C (100.4 F) or greater. In our recommendations we use a cutoff of 38 C for evaluation of infants < 3 months for fever and a cutoff of 39 C (102.2 F) for older children.

While viral infections are the most common cause of fever in young infants, neonates less than 28 days have a particularly higher risk of invasive bacterial infection (up to 14%)12 This document aims to provide a risk-stratified method of distinguishing low risk vs high risk of invasive bacterial infection based on age, clinical appearance, and specific risk factors for certain bacterial infections. These pathways should not be used for the ill appearing young infant who by definition is considered higher risk for invasive bacterial infection.34

Etiology

Neonates are most commonly infected via perinatal vertical transmission or postnatal exposure to organisms. Perinatal vertical transmission usually manifests within 48 to 72 hours after birth. Early-onset sepsis is defined as occurring within the first week of life and late-onset sepsis occurs beyond 7 days of age. Group B Streptococcus used to be the predominant pathogen in neonatal sepsis in the 1970s but with GBS screening and intrapartum antibiotic prophylaxis, there has been an approximate 80% reduction in Group B Streptococcal infection rates. Now, gram-negative pathogens are the cause of infection in about 80% of young infants. Escherichia coli and Klebsiella pneumoniae are noted to be the most common gram-negative pathogens and Staphylococcus aureus, Group B Streptococcus, and Enterococcus spp. as the most common gram-positive pathogens. The majority of bacterial infections in this patient population are identified as urinary tract infections.
Guideline Eligibility Criteria

Neonates and Infants without underlying conditions
Rectal temp ≥100.4°F (38°C) OR reported temp (axillary or rectal) of ≥ 100.4°F (38°C) in the home setting
Hypothermia as defined as rectal temp < 96.8°F (36°C)

Guideline Exclusion Criteria

Toxic/Septic Appearance
Currently receiving antibiotic treatment
Infants with a history of prematurity
Underlying conditions that affect immunity or may otherwise have increased risk of SBO (e.g. VP shunt, central venous catheters).
With an identified focus of infection (e.g. cellulitis, acute otitis media in infants >28 days old)

Differential Diagnosis

Fever in the young infant most often raises the concern for underlying infection. Other causes of fever, such as environmental or toxin exposure should be sought in the history.

Etiologic causes of infection in the infant less than 90 d of age is a dynamic subject. Changes in pediatric medical practice over the past 20 years such as the use of new immunizations have had an impact on the epidemiology of various infections. These include the routine use of rotavirus vaccine, influenza vaccination of mothers, pneumococcal, Haemophilus influenza and varicella vaccines. In addition, widespread Group B streptococcal screening and intrapartum maternal antibiotic therapy has had an impact on the prevalence of Group B streptococcal infections. Ages, appearance, comorbidities, prematurity < 37 weeks gestation, height of fever, history of specific exposures to antibiotics are all risk factors for the presence of infection. 7,8

The etiologies for infectious causes of the febrile infant less than 90 days old include:

Viral Infections

- These infections are the most common cause of fever in young infants. Studies of febrile young infants, including neonates, support an identifiable viral etiology in 17-35% of patients. 5,6
- Acquisition may be vertical from the mother in utero, during the birth process or exposure after birth to close family members and community
- Viruses can cause increased morbidity in young infants due to specific deficiencies in their functional immune system.
- Viruses that are important agents include HSV, Enterovirus, CMV, Varicella, RSV, Influenza, and Adenovirus.
Bacterial Infections

- Invasive and serious bacterial infections in infants include urinary tract infections, blood stream infections, pneumonia, meningitis, omphalitis, skin and soft tissues infections, bone and joint infections, and gastroenteritis.
- These agents account for 10-14% of infections in the young febrile infant. 5,6
- Invasive bacterial infection can be caused by Gram negatives such as E coli, Enterobacter, Klebsiella, Salmonella and Gram positives such as Group B streptococci, S. aureus, S. epidermidis, Listeria, Enterococcus. 9,10
- E coli is the most common bacterial infection in the young febrile infant and is the primary cause of UTI in this age group. 9,10

The prevalence of GBS is decreasing with the advent of widespread maternal screening and intrapartum prophylaxis for this infection. S. aureus is important in skin and soft tissue infection; S epidermidis may play a role in preterm infants. 9,10

Recommendations

<table>
<thead>
<tr>
<th>Evidence Supports</th>
<th>Evidence Lacking/Inconclusive</th>
<th>Evidence Against</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow antibiotic coverage for patients 0-28 days with low risk of meningitis.</td>
<td>Patients 0-28 days: Ampicillin and Gentamicin as a first line therapy with Cefotaxime/Cefepime and Ampicillin used in patients with high suspicion of meningitis. Antibiotic choices are also based on local susceptibilities.</td>
<td>Necessity of lumbar puncture in patients greater than 28 days of age.</td>
</tr>
<tr>
<td>Cohort patients 0-28 days into subgroups that should have HSV workup or not.</td>
<td>Monitoring cultures for 36 hours.</td>
<td></td>
</tr>
<tr>
<td>Cohort patient 29-60 days into subgroups by risk of SBI.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not getting LP in patients 29-60 days at low risk of SBI.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients 28-60 days: Use of ceftriaxone to as outpatient management in patients at low risk for SBI and HSV.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fever Without a Source
Age: 0-28 Day Pathway - Emergency Department
Evidence Based Outcome Center

**EXCLUSION CRITERIA**
- Toxic appearing
- No fever
- Born < 37 weeks gestational age

! ALERT
Patient Toxic/Septic Appearance
Full Sepsis Workup & treat as appropriate.
(LINK TO SEPSIS PATHWAY/GUIDELINE)

**INCLUSION CRITERIA**
Non-toxic with temperature > 38°C (100.4°F) OR < 36°C (96.5°F) measured in Emergency Department OR reported measurement at home.

**ALERT**
Patient Toxic/Septic Appearance
Full Sepsis Workup & treat as appropriate.
(LINK TO SEPSIS PATHWAY/GUIDELINE)

**Order labs:**
- Complete Blood Count with differential
- Blood Culture
- Complete Metabolic Panel
- Urinalysis with Micro
- Urine Culture: Catheter or Suprapubic
- Cerebrospinal Fluid (Hold Tube # 4)
  - Gram stain
  - Culture
  - Cell count with differential
  - Glucose
  - Protein
- Stool culture & Stool WBC (If patient has diarrhea)

**Herpes Simplex Virus (HSV) work-up indicated**

YES

**Start empiric antibiotic treatment:**
Ampicillin x1 + Gentamicin x1

NO

**CSF Pleocytosis and suspicion of meningitis**
OR

CSF Gram stain positive

NO

**YES**

**ADD antiviral treatment:**
Acyclovir

**Contraindications for Ceftriaxone in patients < 28 days of age:**
- Patient expected to or receiving calcium containing IV products.
- Total Bilirubin > 10 (See risk factors for hyperbilirubinemia)

**History and Clinical Features**
- Severe illness / Hypothermia / Lethargy
- Seizures
- Hepatosplenomegaly
- Postnatal HSV contact
- Vesicular rash
- Conjunctivitis
- Interstitial pneumonitis

**Laboratory Findings**
- Thrombocytopenia
- CSF pleocytosis
- without clear bacterial infection
- Transaminitis

**Normal CSF Values**
- 0-20 WBC/mm³
- Protein 0 - 30 days: < 100 mg/dL
- Normal Gram Stain

For questions concerning this pathway, Click Here
Last Updated October 25, 2017
Fever Without a Source
Age: 29-60 Day Pathway - Emergency Department
Evidence Based Outcome Center

**EXCLUSION CRITERIA**
- Toxic appearing
- No fever
- Born ≤ 37 weeks gestational age

**Low Risk Criteria for Serious Bacterial Infection**

**Historical and Clinical Features**
- 29-60 days
- Full-term (≥ 37 weeks gestation)
- No prolonged NICU stay
- No chronic medical problems
- No systemic antibiotics within 72 hours
- Well-appearing and easily consolable
- No focal infections on exam

**Fecal Leucocytes**
- Stool WBC ≤ 5 hpf

**Blood**
- WBC ≥ 5,000 AND ≤ 15,000
- Immature WBC/neutrophil Ratio < 0.2
- Absolute Band Count < 1500/mm³

**Standard UA:**
- WBC < 5/HPF
- Negative LE, Nitrite, Bacteria

**Chest X-ray (if obtained)**
- No infiltrate

**Normal CSF Values**
- 0-20 WBC/mm³
- Protein 0 - 30 days: < 100 mg/dL
- Normal Gram Stain

**INCLUSION CRITERIA**
Non-toxic with temperature > 38°C (100.4°F) OR < 36°C (96.5°F) measured in Emergency Department OR reported measurement at home.

**Manage OFF-PATHWAY**

**Focal bacterial infection**

**Order labs:**
- Complete Blood Count with differential
- Blood Culture
- Basic metabolic panel
- Urinalysis with Micro
- Urine Culture: Catheter or Suprapubic
- Stool culture & Stool WBC (if patient has diarrhea)

**Meets Low Risk Criteria**

**DISCHARGE Home**
Follow-up in 24 hours
No Antibiotics

CSF Collected

**CSF Pleocytosis and suspicion of meningitis**

**OPTION 1**
- Empiric antibiotic treatment: Ceftriaxone

**OPTION 2**
- Patient family & PCP must be in agreement

**OPTION 3**
- Empiric antibiotic treatment: Ceftriaxone + Vancomycin

**ADMIT for Observation**

**ADMIT to Inpatient**
Manage OFF-PATHWAY

**ALERT**

Patient Toxic/Septic Appearance
Full Sepsis Workup & treat as appropriate. (LINK TO SEPSIS PATHWAY/GUIDELINE)

For questions concerning this pathway, Click Here
Last Updated October 25, 2017
Fever Without Source
Inpatient Pathway 0-89 Days of Age
Evidence Based Outcome Center

**EXCLUSION CRITERIA**
- Toxic appearing
- No fever
- Born < 37 weeks gestational age

**INCLUSION CRITERIA**
Non-toxic with temperature > 38°C (100.4°F) OR < 36°C measured in Emergency Department OR reported measurement at home.

**Normal CSF Values**
- 0-20 WBC/mm³
- Protein 0 - 30 days: < 100 mg/dL
- Normal Gram Stain

**0 – 7 Days of Age**
- CSF Pleocytosis and suspicion of meningitis
- OR
- CSF Gram stain positive

**Change antibiotic treatment:**
- ① Meningitic dose of Ampicillin
- ② Cefotaxime
  (Use Cefepime if unavailable)

**ADD antiviral treatment:**
- Acyclovir (If clinical suspicion of HSV)

**Observation – 36 hours**
(Longer if ill-appearing)

- Monitor Cultures:
  - Blood
  - Urine
  - CSF

**8 – 28 Days of Age**
- CSF Pleocytosis and suspicion of meningitis
- OR
- CSF Gram stain positive

**Contraindication for Ceftriaxone?**
- YES

**Change antibiotic treatment:**
- ① Meningitic dose of Ampicillin
- ② Add Ceftriaxone

**ADD antiviral treatment:**
- Acyclovir (If clinical suspicion of HSV)

**Observation: 24-36 hours**
(Longer if ill-appearing)

- Monitor Cultures:
  - Blood
  - Urine
  - CSF

**29 – 89 Days of Age**
- CSF Pleocytosis and suspicion of meningitis
- OR
- CSF Gram stain positive

**Contraindication for Ceftriaxone?**
- NO

**ADD antiviral treatment:**
- Acyclovir (If clinical suspicion of HSV)

**Observation: 24-36 hours**
(Longer if ill-appearing)

- Monitor Cultures:
  - Blood
  - Urine
  - CSF

**Risk factors for hyperbilirubinemia**
- ABO incompatibility
- HDN
- Lethargy
- Temperature instability
- Sepsis
- Acidosis
- Albumin < 3g/dL
- Dehydration
- Weight loss
- Poor feeding
- Irritability
- Jaundice

**Contraindications for Ceftriaxone in patients < 28 days of age:**
- Patient expected to or receiving calcium containing IV products.
- Total Bilirubin > 10 (See risk factors for hyperbilirubinemia)

**Inpatient Discharge Criteria**
- Blood, urine, CSF, & HSV evaluation negative
- Clinically stable based on provider assessment
- Reliable PCP Follow-up
- Education complete

**manage OFF-PATHWAY**

**DISCHARGE Home**
Follow-up in 24 hours

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Last Updated October 25, 2017
### Fever Without a Source
#### Risk Factors for UTI and Screening Recommendations

**Evidence Based Outcome Center**

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**Fever Without a Source**

<table>
<thead>
<tr>
<th>&gt; 2 months – Not Toilet Trained</th>
<th>Toilet Trained – 18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probability of UTI &gt; 1%:</strong></td>
<td><strong>All Patients</strong></td>
</tr>
<tr>
<td>2 or more risk factors</td>
<td>Symptoms referable to urinary tract</td>
</tr>
<tr>
<td><strong>Female Risk Factors</strong>*</td>
<td>Prior history of UTI, fever ≥ 2 days</td>
</tr>
<tr>
<td>Non-black</td>
<td>Prolonged fever (≥ 5 days)</td>
</tr>
<tr>
<td>T ≥ 39°C</td>
<td>Recommend screening for any of the above factors</td>
</tr>
<tr>
<td>Fever ≥ 2 days</td>
<td></td>
</tr>
<tr>
<td>No apparent source of fever</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 12 months</td>
<td></td>
</tr>
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*Recommend screening if prior history of UTI, fever ≥ 2 days

<table>
<thead>
<tr>
<th><strong>Probability of UTI &gt; 1%:</strong></th>
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<tbody>
<tr>
<td>Uncircumcised</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Circumcised with 3 or more Risk Factors</td>
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**Male Risk Factors***

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<tr>
<td>No apparent source of fever</td>
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<tr>
<td>Age &lt; 6 months</td>
</tr>
</tbody>
</table>

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*Recommend screening if prior history of UTI, fever ≥ 2 days*

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**Emergency Department Pathway**

- 0-28 Days
- 29-60 Days
- 2-6 Months

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**Inpatient Pathway**

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For questions concerning this pathway, Click Here

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<table>
<thead>
<tr>
<th>Low Risk Criteria for Serious Bacterial Infection</th>
</tr>
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<tr>
<td>Historical and Clinical Features</td>
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<tr>
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<td>Negative LE, Nitrite, Bacteria</td>
</tr>
<tr>
<td>Chest X-ray (if obtained)</td>
</tr>
<tr>
<td>No infiltrate</td>
</tr>
</tbody>
</table>

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Last Updated October 25, 2017
Patients with any of the following conditions should be considered for a Herpes Simplex Virus work up and empiric treatment:

### Historical and Clinical Features
- Severe illness / Hypothermia / Lethargy
- Seizures
- Hepatosplenomegaly
- Postnatal HSV contact
- Vesicular rash
- Conjunctivitis
-Interstitial pneumonitis

### Laboratory Findings
- Thrombocytopenia
- CSF pleocytosis
- without clear bacterial infection
- Transaminitis

---

**Herpes Simplex Virus Workup Consists of the following labs:**
- ✔️ HSV DNA PCR of Blood
- ✔️ Meningitis/Encephalitis PCR Panel of CSF
- ✔️ Swab/scraping of skin or mucous membrane lesions for HSV DFA AND HSV culture
- ✔️ Surface HSV cultures in viral transport media tube
  - ✔️ Conjunctiva
  - ✔️ Throat
  - ✔️ Nasopharynx
  - ✔️ Rectum
  - ✔️ Skin vesicle (if present)
DCMC Positive Urinalysis (UA) Definition: The presence of Leukocyte Esterase OR Nitrites OR microscopic analysis results positive for leukocytes or bacteria is suggestive of an active UTI. When more than one of these findings is present at the same time, the sensitivity and specificity increase significantly.

Dell Children’s and Seton Family of Hospitals does not currently perform an enhanced urinalysis on urine specimens routinely. The following criteria are guide in diagnosing a UTI in young children using the standard method of collection and processing.

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Interpretation</th>
</tr>
</thead>
</table>
| Nitrites            | • Poor sensitivity: Conversion of nitrates to nitrites by bacteria takes approximately 4 hours and not all bacteria reduce nitrate levels combined with frequency of infants voiding.  
                      • Helpful when positive. Few false positives and high specificity. |
| Leukocyte Esterase  | • Positive leukocyte esterase is suggestive of a UTI. However, children may have WBC present in their urine in conditions other than a UTI (e.g. Kawasaki Disease) |
| White Blood Cells   | Positive if:                                                                  |
| (WBC) - Pyuria      | • ≥ 5 WBC per HBF via standard method                                           |
|                     | Pyuria is absent in approximately 10% of children with a UTI                  |
| Bacteriuria         | Presence of bacteriuria alone in the absence of other findings does not define a UTI. |

**Culture**

<table>
<thead>
<tr>
<th>Method</th>
<th>Definite*</th>
<th>Indeterminant†</th>
<th>Contaminant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suprapubic</td>
<td>Any growth</td>
<td></td>
<td>Growth of non-pathogens, Mixed culture</td>
</tr>
<tr>
<td>Catheter</td>
<td>≥ 50,000 CFU/ML</td>
<td>≥ 10,000 CFU/ML</td>
<td>Growth of non-pathogens, Mixed culture, &lt; 10,000 CFU/ml</td>
</tr>
</tbody>
</table>

* If also with presence of pyuria or bacteriuria  
† Consider obtaining repeat specimen

Mixed Culture = uropathogen + non-pathogen or two uropathogens
Bag UA specimens should never be sent for urine culture. Only catheter or suprapubic methods are appropriate for culture collection in this age.

**Uropathogens**

<table>
<thead>
<tr>
<th>Gram Negative</th>
<th>Gram Positive</th>
<th>Non-pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli (~80%)</td>
<td>Staphylococcus saprophyticus</td>
<td>Lactobacillus</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>Enterococcus</td>
<td>Coagulase-negative Staph</td>
</tr>
<tr>
<td>Proteus</td>
<td>Staphylococcus aureus</td>
<td>Corynebacterium</td>
</tr>
<tr>
<td>Enterobacter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrobacter</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For questions concerning this pathway,  
Click Here  
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<table>
<thead>
<tr>
<th>Drug</th>
<th>NON-MENINGITIC ≤ 7 days of age</th>
<th>NON-MENINGITIC &gt; 7 days of age</th>
<th>MENINGITIC ≤ 7 days of age</th>
<th>MENINGITIC &gt; 7 days of age</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>50 mg/kg/dose IV q8h</td>
<td>50 mg/kg/dose IV q6h</td>
<td>100 mg/kg/dose IV q8h</td>
<td>100 mg/kg/dose IV q6h</td>
<td>5 doses</td>
</tr>
<tr>
<td>Cefepime</td>
<td>50 mg/kg/dose IV q8h</td>
<td>50 mg/kg/dose q8h</td>
<td>50 mg/kg/dose q6h</td>
<td>50 mg/kg/dose q6h</td>
<td>5 doses</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>≤ 7 days of age: 50 mg/kg/dose q8h</td>
<td>&gt; 7 days of age: 50 mg/kg/dose q6h</td>
<td>50 mg/kg/dose q8h</td>
<td>50 mg/kg/dose q6h</td>
<td>5 doses</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>If to be admitted: 50 mg/kg/dose q12h</td>
<td>If to be discharged: 50-100 mg/kg/dose IV (ED ONLY)</td>
<td>50 mg/kg/dose q8h</td>
<td>50 mg/kg/dose q6h</td>
<td>3 doses</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4 mg/kg/dose IV q24h</td>
<td>4 mg/kg/dose IV q24h</td>
<td>4 mg/kg/dose IV q24h</td>
<td>4 mg/kg/dose IV q24h</td>
<td>2 doses</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>≤ 7 days of age: 20 mg/kg/dose IV q8h</td>
<td>&gt; 7 days of age: 20 mg/kg/dose IV q6h</td>
<td>20 mg/kg/dose IV q8h</td>
<td>20 mg/kg/dose IV q6h</td>
<td>5 doses</td>
</tr>
</tbody>
</table>

### Recommended Dose for UTI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>17 mg/kg/dose q8h</td>
<td>7 Days</td>
</tr>
</tbody>
</table>

### Recommended Dose for Antiviral

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>20 mg/kg/dose IV q8h</td>
<td>5 doses OR until HSV surface cultures AND PCR Blood &amp; CSF negative Exceptions: Seizures, Lethargy, or ongoing Fever</td>
</tr>
</tbody>
</table>

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*a* Dosing in this table is for patients with normal renal function. Please contact pharmacy for assistance with dosing in renal insufficiency.

*For gentamicin, serum drug levels are not necessary unless treatment is anticipated or continued for more than 2 doses, SCr is increased more than 0.3 mg/dL from normal value for age, or UOP less than 1 ml/kg/hr.*

*For vancomycin, serum drug levels are not necessary unless treatment is anticipated or continued for more than 2 doses, SCr is increased more than 0.3 mg/dL from normal value for age, or UOP less than 1 ml/kg/hr.*

*If cultures become positive at any time, treat specific condition, narrow agent and lengthen antibiotic duration as appropriate.*
Diagnostic Evaluation

Clinical presentation

1. Fever (>38°C or 100.4°F rectally) without clinically identifiable source in infants age 0-60 days of life
   -OR-
2. Hypothermia¹ (<36°C) without clinically identifiable source in infants age 0-60 days of life
   Applies to temperature measured in Emergency Department or reported from home

Laboratory Tests

Laboratory tests, though some may be non-specific, can provide evidence towards a potential serious bacterial infection (SBI) or other viral pathology as the fever source, prompting further evaluation and treatment

1. Complete blood count (CBC)
   a. Leukocytosis or leukopenia defined as white blood cell (WBC) count >15,000/mm³ or <5,000/mm³
   b. Increased immature cells (presence of bands or “left shift”)
   c. Thrombocytopenia (Platelet count <100,000/mm³) can be seen in severe sepsis or secondary to a viral process
2. Complete metabolic panel
   a. In patients with severe sepsis, acidosis, electrolyte disturbances, elevation in serum creatinine, hypoalbuminemia and transaminitis can be seen
   b. Transaminitis can also be seen with certain viral infections such as disseminated Herpes simplex virus
   c. If dosing ceftriaxone in patient under 28 days of life, consider screening total bilirubin due to risk of bilirubin displacement
3. Urinalysis with Micro
   a. Pyuria (>5 WBC per HPF via standard method and/or positive leukocyte esterase) provides evidence of urinary tract inflammation, most commonly from acute cystitis or pyelonephritis
   b. Nitrites can indicate presence of certain gram negative bacteria within the urine, though generally have a low sensitivity for diagnosis of cystitis or pyelonephritis specifically
4. Cerebrospinal fluid (CSF) analysis
   a. CSF pleocytosis (increased WBC count) according to age specific norms indicates inflammatory process most commonly seen with infectious etiologies such as meningitis or meningoencephalitis

<table>
<thead>
<tr>
<th>Normal CSF WBC values based on age</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-28 days</td>
</tr>
<tr>
<td>≥ 29 days</td>
</tr>
</tbody>
</table>
b. Increased protein can be seen in the setting of meningitis or meningoencephalitis

<table>
<thead>
<tr>
<th>Normal CSF protein values based on age</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30 days</td>
</tr>
<tr>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>&gt; 30 days</td>
</tr>
<tr>
<td>15-45 mg/dL</td>
</tr>
</tbody>
</table>

c. Glucose can be decreased in acute bacterial meningitis

<table>
<thead>
<tr>
<th>Normal CSF Glucose values based on age</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-28 days</td>
</tr>
<tr>
<td>34-119 mg/dL</td>
</tr>
<tr>
<td>≥ 29 days</td>
</tr>
<tr>
<td>40-80 mg/dL</td>
</tr>
</tbody>
</table>

d. Gram stain can provide evidence of bacterial pathogens present in CNS

5. Cultures
   a. Cultures of blood, urine and CSF should be obtained to rule out presence of bacterial pathogen
   b. Stool culture can be considered in patient where significant diarrhea is present to rule out bacterial pathogen. Fecal WBCs can be seen in significant colitis as well as other non-infectious sources.

6. Molecular diagnostics
   a. Herpes simplex virus – if concerned for acute HSV disease, following workup should be obtained for complete evaluation
      i. HSV PCR blood
      ii. HSV PCR CSF (can be included in Biofire – see section d.)
      iii. HSV surface cultures
   b. Enterovirus PCR in CSF can provide etiology of pleocytosis in the absence of positive bacterial culture (can be included in Biofire – see section d.)
   c. Rapid viral testing for Influenza and RSV, when taken in context of correlating clinical symptoms and community prevalence can provide evidence of a fever source in the absence of suspected SBI.
   d. PCR panels (Respiratory pathogen panel, Biofire of CSF) provide rapid PCR testing for a variety of bacterial and viral pathogens and can be helpful in identifying fever source in cases where positive results would affect clinical management and potential outcomes such as
      i. Antibiotic pretreatment where bacterial culture may not be reliable
      ii. Initiation of antimicrobials (HSV encephalitis, mycoplasma pneumonia, pertussis, etc)

Imaging
Chest X-Ray can be considered if concerned for an acute lower respiratory tract infection based on clinical symptoms.

Methods

Existing External Guidelines/Clinical Pathways
Existing External Guideline/Clinical Pathway | Organization and Author | Last Update
---|---|---
Fever Without Localizing Signs | Texas Children’s Hospital | 2009
Neonatal Fever Pathway | Seattle Children’s | 2017
Febrile Infant Clinical Pathway | Children’s Hospital of Philadelphia | 2015

Any published clinical guidelines have been evaluated for this review using the AGREE II criteria. The comparisons of these guidelines are found at the end of this document. AGREE II criteria include evaluation of: Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity of Presentation, Applicability, and Editorial Independence.

Review of Relevant Evidence: Search Strategies and Databases Reviewed

<table>
<thead>
<tr>
<th>Search Strategies</th>
<th>Document Strategies Used</th>
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<tbody>
<tr>
<td>Search Terms Used:</td>
<td>Infant, neonate, less than 7 days of age, 28 days of age, risk of serious bacterial infections, herpes simplex virus, risk stratification, blood stream infection, enterovirus, antibiotic course, septic workup, sepsis, positive urine analysis, lumbar puncture, hospital admission, antibiotic management</td>
</tr>
<tr>
<td>Years Searched - All Questions</td>
<td>2007 - 2017</td>
</tr>
<tr>
<td>Language</td>
<td>English</td>
</tr>
<tr>
<td>Age of Subjects</td>
<td>0 – 6 Months of age</td>
</tr>
<tr>
<td>Search Engines</td>
<td>PubMed, Cochrane, Google</td>
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<tr>
<td>Government/State Agencies</td>
<td>National Guideline Clearinghouse</td>
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</table>

Evidence Found with Searches

<table>
<thead>
<tr>
<th>Check Type of Evidence Found</th>
<th>Summary of Evidence – All Questions</th>
<th>Number of Articles Obtained</th>
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<tbody>
<tr>
<td>☐</td>
<td>Systematic Reviews</td>
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<td>Meta-analysis articles</td>
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<td>☒</td>
<td>Randomized Controlled Trials</td>
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<td>☒</td>
<td>Non-randomized studies</td>
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<tr>
<td>☐</td>
<td>Review articles</td>
<td></td>
</tr>
<tr>
<td>☐</td>
<td>Government/State agency regulations</td>
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</tr>
<tr>
<td>☐</td>
<td>Professional organization guidelines, white papers, ect.</td>
<td></td>
</tr>
<tr>
<td>☐</td>
<td>Other:</td>
<td></td>
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</table>

Evaluating the Quality of the Evidence
The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Type of Evidence</th>
</tr>
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<tbody>
<tr>
<td>Strong</td>
<td>Desirable effects clearly outweigh undesirable effects or vice versa</td>
</tr>
<tr>
<td>Weak</td>
<td>Desirable effects closely balanced with undesirable effects</td>
</tr>
<tr>
<td>High</td>
<td>Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies</td>
</tr>
<tr>
<td>Moderate</td>
<td>Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies</td>
</tr>
<tr>
<td>Low</td>
<td>Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence</td>
</tr>
<tr>
<td>Very Low</td>
<td>Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence</td>
</tr>
</tbody>
</table>
Executive Summary

Clinical Standards Preparation
This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team.

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Recommendations
Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible.

Approval Process
EBOC guidelines are reviewed by DCMC content experts, the EBOC committee, and are subject to a hospital wide review prior to implementation. Recommendations are reviewed and adjusted based on local expertise.

Evaluating the Quality of the Evidence
Published clinical guidelines were evaluated for this review using the AGREE II criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. This clinical standard specifically summarizes the evidence in support of or against specific interventions and identifies where evidence is lacking/inconclusive. The following categories describe how research findings provide support for treatment interventions.

“Evidence Supports” provides evidence to support an intervention
“Evidence Against” provides evidence against an intervention.
“Evidence Lacking/Inconclusive” indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn from the evidence.

Disclaimer
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References

12. A. Martinez Planas; C. Munoz Almagro. Clinical Microbiology and Infection 2012; 18: 856-861. Low prevalence of invasive bacterial infection in febrile infants under 3 months of age with enterovirus infection
44. Cincinnati Children’s Hospital Medical Center. “Fever of Uncertain Source”. 2010
45. Diagnosis and management of febrile infants (0-3 months). http://www.ahrq.gov/clinic/tp/febrinftp.htm; Updated 2012.