**Definition:** An acute febrile illness (temperature ≥100.4°F (38°C)) with uncertain etiology after completion of a thorough history and physical examination. (1-4)

**Etiology:** The most common cause of fever without localizing signs (FWLS) is a viral infection. The challenge lies in the difficulty of distinguishing serious bacterial illness (SBI) from viral illness in neonates and early infancy. (1,4-6)

**Inclusion Criteria:**
- Age 0-60 days (Term infants ≥37 weeks gestation)
- Neonates and infants without underlying conditions
- Actual rectal temp ≥100.4°F (38°C) OR reported temp (axillary or rectal) of ≥100.4°F (38°C) in home setting

**Exclusion Criteria:**
- History of prematurity
- Underlying conditions that affect immunity or may otherwise increase risk of SBI
- Toxic/Septic appearance
- Receiving antibiotic treatment for FWLS
- Routine vaccinations given within the previous 48 hours
- Presenting with seizures
- Requiring intensive care management
- Identified focus of infection (e.g., cellulitis, acute otitis media in infants >28 days old)

**Differential Diagnosis:**
- Meningitis
- Bone and joint infections
- Urinary tract infection
- Pneumonia
- Sepsis/Bacteremia
- Enteritis
- Herpes Simplex Virus (HSV) infection
- Enterovirus
- Parechovirus

**Toxic Criteria** (7,8)
Infants that meet ANY of the toxic criteria should receive a full sepsis workup and be admitted to the inpatient area for antibiotic therapy and observation (See Tables 1 & 2).

**Signs/Symptoms include:**
- Poor perfusion
- Capillary refill time >2 seconds
- Cyanosis
- Lethargy
- Unable to console
- Tachypnea or bradypnea
- Hypothermia (96.8°F/36°C)

### Table 1. Signs and Symptoms of Shock (9,10)

<table>
<thead>
<tr>
<th></th>
<th>Cold Shock</th>
<th>Warm Shock</th>
<th>Non-specific</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulses</strong> (central vs. peripheral)</td>
<td>Decreased or weak</td>
<td>Bounding</td>
<td></td>
</tr>
<tr>
<td><strong>Capillary refill</strong> (central vs. peripheral)</td>
<td>≥3 sec</td>
<td>Flash (&lt;1 sec)</td>
<td></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Mottled, cool</td>
<td>Flushed, erythoderm (other than face)</td>
<td>Petechiae below the nipple, any purpura</td>
</tr>
<tr>
<td><strong>Mental status</strong></td>
<td>Decreased, irritability, confusion inappropriate crying or drowsiness, poor interaction with parents, lethargy, diminished arousability, obtunded</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*↑ HR followed by ↓ HR with BP changes will be noted as shock becomes uncompensated.

### Table 2. Vital Sign Changes of Sepsis (9,10)

<table>
<thead>
<tr>
<th>Age</th>
<th>Heart Rate</th>
<th>Respiratory Rate</th>
<th>Systolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0d - 1m</td>
<td>&gt;205</td>
<td>&gt;60</td>
<td>&lt;60</td>
</tr>
<tr>
<td>&gt;1m to 3m</td>
<td>&gt;205</td>
<td>&gt;60</td>
<td>&lt;70</td>
</tr>
</tbody>
</table>

†BP changes are late signs of worsening condition. May also present with chills.

**Diagnostic Evaluation:** In this age group, bacterial pathogens associated with FWLS may include Gram-positive organisms (such as group B Streptococcus, Enterococcus, group A Streptococcus, Staphylococcus aureus, Listeria monocytogenes) and Gram-negative organisms (such as Escherichia coli, Enterobacter, Klebsiella). Streptococcus pneumoniae is more likely to occur in infants >30 days old. (11-12)

Viral pathogens, such as enterovirus, adenovirus, herpes simplex virus, influenza virus, and parainfluenza virus, are also a concern in this patient population. (13,14)

**History:** Assess for
- Onset of fever
- Immunization status (15)
- Irritability
- Poor feeding
- Decreased urine output
- Exposure to infectious agents
- Other sick contacts/family members
- Maternal fever at time of delivery
• Maternal Group B streptococcal vaginal colonization
• Maternal HSV infection

Physical Examination:
Rectal temperatures are preferred to axillary or other methods
of temperature measurements.
A thorough clinical history and physical examination are
essential to determine risk of SBI or identify focus of infection.

Table 3. Laboratory Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>0-28 days</th>
<th>29 to 60 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count (CBC) with differential and platelets</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood culture (BC) (obtain prior to antibiotic administration)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Enterovirus CSF PCR (during peak season of May – October)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis (UA) with micro and culture (obtain specimen via cath or SPA† only)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lumbar puncture* (LP) [gram stain, culture, cell count and diff, glucose, protein, viral culture†]</td>
<td>X</td>
<td>Optional</td>
</tr>
</tbody>
</table>

Consider: (19-24)

- Stool for culture and presence of WBCs (if diarrhea present)
- Viral diagnostic testing or rapid tests (if respiratory symptoms)
- Chest X-ray (if respiratory symptoms; WBC >20,000/mm³ or ANC >10,000/mm³)
- Herpes simplex virus (HSV) if risk factors present or patient not improving on antibiotics
- Blood and/or CSF parechovirus PCR during peak season - May to October (if febrile and other viral/bacterial cultures negative)

† Cath (transurethral catheterization) or SPA (suprapubic aspiration)
‡ Tube #1 Glucose, protein
Tube #2 Cell count & diff, Gram stain & culture
HOLD Tube #3 in virology lab

For infants with FWLS, laboratory evaluation for neonatal HSV infections should be reserved primarily for those with clinical findings suggestive of an HSV infection or a prior history of HSV. (25-28)

HSV Risk Factors (27)
- Maternal primary HSV infection
- Maternal fever
- Vaginal delivery
- Prematurity
- Neonatal seizures
- Vesicular rash
- CSF pleocytosis (monocytosis)
- Elevated hepatic enzymes

Signs/Symptoms of Systemic HSV (28)
- Skin, eye, and mouth lesions/disease
- Seizures, lethargy, and fever
- Disseminated form- neonate presents with multi-organ failure

The laboratory tests below are recommended if HSV suspected. (27,28)
- CSF specimen for HSV PCR (priority) and viral culture (if adequate specimen available)
- Blood PCR
- Blood viral culture
- Rectal viral culture
- Conjunctiva viral culture
- Nasopharyngeal (NP) viral culture
- ALT/AST

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**Evidence Supports**

- Consider administration of acyclovir for neonates with no identified bacterial pathogen in CSF and the presence of CSF pleocytosis and/or exam, concern or possible maternal history of HSV, and/or toxic appearance. (25,27,29,30) – Weak recommendation, low quality evidence

- The laboratory test that is most accurate in diagnosing HSV is the CSF HSV PCR in the presence of pleocytosis. (31-33) – Strong recommendation, low quality evidence

- Empiric antibiotic therapy of ampicillin and gentamicin for all neonates (0-28 days). If there is a concern for meningitis or CSF pleocytosis, cefTAZidime should be administered in lieu of gentamicin. (34,35) – Strong recommendation, low quality evidence

- The immunogenicity of influenza vaccine in former premature infants is lower than in full term infants. (39) – Strong recommendation, very low quality evidence

- Enterovirus testing should be utilized in addition to usual care in order to decrease length of stay. (37,38) – Strong recommendation, low quality evidence

- All infants 0-60 days with fever without localizing signs should be tested for enterovirus during peak season regardless of the presence of CSF pleocytosis. (*TCH PCR positivity data plus expert consensus indicates that peak season will likely occur from May through October). (38,42) – Strong recommendation, low quality evidence

- Enterovirus CSF PCR should be used for testing when CSF specimen is available. (*This recommendation is also based on rapid turnaround time of CSF PCR as compared to serum PCR at TCH.) (19,42-44) – Strong recommendation, low quality evidence

- For enterovirus-positive infants 0-28 days old, they should have a minimum of 24 hours of hospital monitoring of bacterial cultures if low risk and 48 hours if high risk. (18,19,42) – Weak recommendation, low quality evidence

- For enterovirus-positive infants 29-60 days old, no further inpatient monitoring of bacterial cultures is needed once enterovirus result is known. If otherwise meeting discharge criteria, high risk 29-60 day old infants can be discharged with a dose of ceftriaxone and close pediatrician follow-up. For the low risk enterovirus infant 29-60 days old, they can be discharged as soon as result is known without antibiotics. (*Recommendations based on expert consensus plus epidemiologic evidence showing low rates of SBI. SBI seems more common in neonates and those that are high risk.) (18,19,42) – Weak recommendation, low quality evidence

- Consider CSF parechovirus testing during peak season (May to October) when other viral (e.g., enterovirus, HSV) and bacterial etiologies have been ruled out. (20-23,45,46) – Weak recommendation, low quality evidence

- AST and/or ALT lab tests should not routinely be used for screening for disseminated HSV in all infants 0-28 days with fever. If at any time the child has risk factors for HSV, CSF pleocytosis, appears ill, and/or has a persistent fever with negative bacterial cultures ≥48 hours, additional lab tests, including but not limited to HSV PCR, should be completed. (25,28,47-49) – Strong recommendation, low quality evidence

- Procalcitonin and/or C-reactive protein (CRP) should not be used as predictors of SBI in well-appearing children with FWLS. (50-58) – Strong recommendation, moderate quality evidence

Remarks: Although the sensitivity of procalcitonin has shown to be higher than other biomarkers, there is not enough data to support changes in the clinical management of patients based upon this value alone. At this time, there is not a clearly defined cutoff in the literature for procalcitonin.

**Evidence Against**

- For enterovirus-positive infants 0-28 days old, they should have a minimum of 24 hours of hospital monitoring of bacterial cultures if low risk and 48 hours if high risk. (18,19,42) – Weak recommendation, low quality evidence

- For enterovirus-positive infants 29-60 days old, no further inpatient monitoring of bacterial cultures is needed once enterovirus result is known. If otherwise meeting discharge criteria, high risk 29-60 day old infants can be discharged with a dose of ceftriaxone and close pediatrician follow-up. For the low risk enterovirus infant 29-60 days old, they can be discharged as soon as result is known without antibiotics. (*Recommendations based on expert consensus plus epidemiologic evidence showing low rates of SBI. SBI seems more common in neonates and those that are high risk.) (18,19,42) – Weak recommendation, low quality evidence

- Consider administration of acyclovir for neonates with no identified bacterial pathogen in CSF and the presence of CSF pleocytosis and/or exam, concern or possible maternal history of HSV, and/or toxic appearance. (18,19,42)

**Condition-Specific Elements of Clinical Management**

**Table 4. Low Risk Lab Criteria for 29-60 day old infants**

<table>
<thead>
<tr>
<th>CBC with d/p (cath or SPA specimen)</th>
<th>UA with micro</th>
<th>LP</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 5-15/mm³</td>
<td>Negative for nitrites &amp; leukocyte esterase</td>
<td>0-28 days</td>
</tr>
<tr>
<td>Absolute band count &lt;1500/mm³</td>
<td>WBC &lt;10/hpf</td>
<td>WBC cell count 0-22/mm³</td>
</tr>
<tr>
<td>Clear</td>
<td>Normal protein (0-30 days &lt;100 mg/dL)</td>
<td>≥29 days</td>
</tr>
<tr>
<td>Negative</td>
<td>(≥1 month 15-45 mg/dL)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5. Admission/Outpatient Management Criteria**

<table>
<thead>
<tr>
<th>Neonates (≤28 days):</th>
</tr>
</thead>
</table>
| If presenting in clinic setting, refer to EC. Evaluate with a full sepsis workup, including enterovirus CSF PCR during peak season of May to October, and admitted to the inpatient area for antibiotic therapy and observation. (15,42-44)

- **Empiric antibiotic therapy of ampicillin and gentamicin should be initiated on all neonates. If there is a concern for meningitis or CSF pleocytosis, ampicillin and cefTAZidime should be administered. (25,34,35)**
- **Consider administration of acyclovir for neonates with no identified bacterial pathogen in CSF and the presence of CSF pleocytosis and/or exam, concern or possible maternal history of HSV, and/or toxic appearance. (25,27,29,30)**
- **Enterovirus-positive infants 0-28 days old should have a minimum of 24 hours of hospital monitoring of bacterial cultures if low risk and 48 hours if high risk. (18,19,42)**

- **Infants ≥ 29 days:**
  - **If CBC or UA values do not meet low risk lab criteria, an LP is indicated (Table 4). Antibiotics should not be administered until after LP is obtained.**
  - **Enterovirus-positive infants 29-60 days old should be managed outpatient once enterovirus result is known if meeting all other discharge criteria (Table 5). (18,19,42)**

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DATE: September 2014
• High risk 29-60 day old enterovirus-positive infants can be discharged with a dose of cefTRIAXone and close pediatrician follow-up.
• Low risk enterovirus-positive infants 29-60 days old can be discharged as soon as result is known without antibiotics. A penicillin and a third generation cephalosporin are recommended as first-line therapy. For infants >6 weeks old, clinicians may consider third generation cephalosporin monotherapy. Meningitic dosing should be initiated on all neonates and infants until CSF test results have been reviewed and CNS involvement has been ruled out.

Follow-up Care
Healthcare provider to follow up on blood and urine cultures (if discharged before 48 hours)
Healthcare provider to call lab for CSF culture interpretation prior to discharge.
Follow-up appointment with PCP 12-24 hours post-discharge
Return to PCP/EC if worsening symptoms

Inpatient/Observation Discharge Criteria
• Decreasing fever curves
• Well-appearing with no evolution of signs/symptoms
• Tolerating oral intake and maintaining hydration status
• One of the following clinical situations:
  - Negative cultures after 48 hours and clinically stable (applies only to inpatients)
  - Low risk enterovirus-positive infants 0-28 days with negative bacterial cultures after 24 hours of hospital monitoring
  - Clinically stable infants 29-60 days old with positive urine culture (CSF & blood negative) after 23 hours of observation on PO antibiotics
• Reliable follow-up available 12-24 hours post-discharge
• Caregiver and PCP agree with plan
• Caregiver understands discharge education

Measures
Outcome
• Length of stay
• # of readmissions for same problem
• Type of follow-up post EC or Inpatient discharge (phone call vs. visit to PCP)
• # of infants >28 days with LP vs. no LP based on risk criteria
• EC treatment plan for infants after LP performed vs. infants without LP performed
• # of call backs for positive blood cultures
• # of call backs for positive urine cultures for patients with negative UA
• # of enterovirus positive patients with concomitant serious bacteria infection
### Table 5. Antibiotic Dose Administration Table

**Infants 0-28 days**  
Consider insurance/Medicaid formulary restrictions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Empirical Parenteral Therapy (IV)</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Ampicillin | ≤7 days: 100 mg/kg/dose every 12 h  
>7 days: 50 mg/kg/dose every 6 h  
If concern for meningitis: 75 mg/kg/dose every 6 hours |
| Gentamicin Sulfate | Neonates: 4 mg/kg/dose every 24 h |
| **Use in lieu of gentamicin for suspected meningitis or CSF pleocytosis** | |
| CefTAZidime | Neonates: 0-28 days: 50 mg/kg/dose every 8 h  
NOTE: Recommended usage to:  
- Neonatal patients (defined as ≤44 weeks postmenstrual age OR neonates <1 month of age) |
| **Treatment of choice for suspected Staphylococcus** | |
| Vancomycin | <7 days old:  
>2,000 g: 10 to 15 mg/kg/dose every 8 to 12 hours  
≥7 to 28 days:  
>2,000 g: 10 to 15 mg/kg/dose every 6 to 8 hours |
| **Treatment of choice for Herpes Simplex Virus (HSV)** | |
| Acyclovir | Neonates and Infants:  
20 mg/kg/dose every 8 h |

---

### Table 6. Antibiotic Dose Administration Table

**Infants 29-60 days**  
Consider insurance/Medicaid formulary restrictions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient or Emergency Center Empirical Therapy (IM/IV)</strong></td>
<td></td>
</tr>
<tr>
<td>CefTRIAXone</td>
<td>Infants &gt;28 days: 50 mg/kg/dose once</td>
</tr>
<tr>
<td><strong>Empirical Parenteral Therapy (IV)</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Ampicillin | Infants >28 days and children:  
Mild to Moderate Infection: 100-150 mg/kg/DAY divided every 6 hours  
MAX daily dose: 4000 mg/DAY  
Meningitis or Severe Infection: 200-400 mg/kg/DAY divided every 6 hours; MAX daily dose: 12g/DAY |
| CefTRIAXone | Infants >28 days:  
100 mg/kg/dose every 24 h  
NOTE: Not for use in patients receiving Y-site administration of calcium-containing IV fluids with a single lumen or single IV site  
Not for use in infants <44 weeks postmenstrual age OR neonates <1 month of age  
*Use cefTAZidime as an alternative |
| **Treatment of choice for suspected Staphylococcus** | |
| Vancomycin | Infants >28 days to 60 days:  
15 mg/kg/dose every 8 hours |

1Redeuce antibiotics to general dosing for suspected infection once meningitis ruled out.
TCH Evidence-Based Outcomes Center Clinical Algorithm
Neonates & Infants with Fever Without Localizing Signs (FWLS)
0-28 days

**Exclusion Criteria:**
- History of prematurity
- Underlying conditions that affect immunity or may otherwise increase risk of Serious Bacterial Infection
- Toxic/Septic in appearance
- Currently receiving abx for FWLS
- Received routine immunizations within 48 hours of presentation
- Presents with seizures
- Requires ICU management
- Has an identified focus of infection

**Low Risk Lab Criteria**
- CBC w/ diff & platelets
- WBC 5-15/mm³
- Absolute Band Count < 1500/mm³
- UA w/ micro & culture
- LPI (gram stain, culture, cell count & diff, protein, glucose, HOLD tube #3 in virology if collected)
- Enterovirus PCR (if peak season)
- IV Antibiotics ± (Start ampicillin/gentamicin; if concern for meningitis, use cefTAZidime in lieu of gentamicin)
- If exam, history or concern of HSV send: HSV PCR from CSF and blood, and administer acyclovir
- Consider other viral work-ups
- Admit patient and notify PCP

**OFF algorithm**
- Manage as appropriate to clinical findings

**Presence of toxic criteria**
- Yes
  - OFF algorithm
  - Full sepsis workup & treat as appropriate

**CBC w/ diff**
- Blood cultures
- Surface cultures without lesions
- UA with micro & culture
- LPI (gram stain, culture, cell count & diff, protein, glucose, HOLD tube #3 in virology if collected)
- Enterovirus PCR (if peak season)
- IV Antibiotics ± (Start ampicillin/gentamicin; if concern for meningitis, use cefTAZidime in lieu of gentamicin)
- If exam, history or concern of HSV send: HSV PCR from CSF and blood, and administer acyclovir
- Consider other viral work-ups
- Admit patient and notify PCP

**Exclusion Criteria:**
- History of prematurity
- Underlying conditions that affect immunity or may otherwise increase risk of Serious Bacterial Infection
- Toxic/Septic in appearance
- Currently receiving abx for FWLS
- Received routine immunizations within 48 hours of presentation
- Presents with seizures
- Requires ICU management
- Has an identified focus of infection

**Enterovirus Positive AND presence of low risk lab criteria**
- Yes
  - Monitor in hospital with IV antibiotics.
  - If bacterial cultures negative at 24 hours, patient may be discharged if meeting all other criteria

**If worsening signs/symptoms, consider additional diagnostic testing for alternate source, including but not limited to HSV PCR, and treat as appropriate OFF algorithm**

**Consider discharge if:**
- Reliable EC or PCP follow-up in 12-24 h
- Adequate caregiver education
- PCP & caregiver agree with plan
**TCH Evidence-Based Outcomes Center Clinical Algorithm**

**Neonates & Infants with Fever Without Localizing Signs (FWLS)**

**29-60 days**

**Begin**

- Fever ≥ 100.4°F (38°C)
  - Yes: OFF algorithm
  - Manage as appropriate to clinical findings

- Presence of toxic criteria
  - Yes: OFF algorithm
  - Full sepsis workup & treat as appropriate

- CBC
  - Blood Culture
  - UA with micro & culture^
  - Enterovirus CSF PCR (if peak season)*
  - LP† (optional)

- Enterovirus positive
  - Yes: Presence of low risk lab criteria
  - No: Discharge home if meeting all other discharge criteria

- Presence of low risk lab criteria
  - Yes: Options:
    1. Outpatient plan ± ceftriaxone under the following conditions:
       - Reliable EC or PCP follow-up in 12-24 h
       - Adequate caregiver education
       - PCP & caregiver agree with plan OR
       - Admit & consider empiric abx tx†
    2. LP† if not done
       - Admit and tx with empiric antibiotics
       - Admit on observation status and no antibiotics
       - If admit, notify PCP of patient’s status

- Clinically well & cx neg ≥ 48 h
  - Yes: Treat as appropriate OFF algorithm
  - No: Consider discharge if:
    - Reliable EC or PCP follow-up in 12-24 h
    - Adequate caregiver education
    - PCP & caregiver agree with plan

**Exclusion Criteria:**
- History of prematurity
- Underlying conditions that affect immunity or may otherwise increase risk of Serious Bacterial Infection
- Toxic/Septic in appearance
- Currently receiving abx for FWLS
- Received routine immunizations within 48 hours of presentation
- Presents with seizures
- Requires ICU management
- Has an identified focus of infection

**Septic Shock Criteria**
- Immediately refer to the Septic Shock guideline and intervene rapidly if patient has toxic-appearance, ill-appearance, altered mental status, and/or compromised perfusion with abnormal vital signs

**Low Risk Lab Criteria**

- CBC w/ diff & plat
  - WBC 5-15/mm^3
  - Absolute Band Count < 1500/mm^3
- Urinalysis
  - Clear
  - Negative for nitrites & leukocyte esterase
  - WBC < 10/hpf
- Lumbar Puncture
  - 0-28 days
    - WBC cell count 0-22/mm^3
    - ≥ 29 days
      - WBC cell count 0-7/mm^3
      - Normal protein (0-30 days < 100 mg/dL)
      - (> 1 month 15-45 mg/dL)

- Enterovirus positive
  - Presence of low risk lab criteria
  - Discharge home if meeting all other discharge criteria

- Give a dose of ceftriaxone
- Discharge home if meeting all other discharge criteria

^Obtain urine specimen via cath or SPA only
*Enterovirus Peak season – May through October
†Antibiotics should not be administered until after LP is obtained

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References

1. Cincinnati Children’s Hospital. (2010). Evidence-based care guideline for fever of uncertain source in infants 60 days of age or less.


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Clinical Standards Preparation
This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children’s Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

Fever Without Localizing Signs 0-60 Days Content Expert Team
Aderonke Adekunle-Ojo, MD, Emergency Medicine
Joseph Allen, MD, Medical Director, EC West Campus
Rebecca Anderson, MSN, RN, CPNP, Texas Children’s Pediatrics
Kim Dinh, PharmD, Pharmacy
James Dunn, PhD, Pathology
Susan Engleman, PNP, West Campus
Al Gest, MD, Neonatology
Leslie Harris, MD, Neonatology
Lucila Marquez, MD, Pediatric Hospital Medicine
Aimea Montillo, RN, Nurse Manager, EC
Brent Mothner, MD, Hospital Medicine
Debra Palazzi, MD, Infectious Disease
Michael Speer, MD, Neonatology
Stanley Spinner, MD, Chief Medical Officer, Texas Children’s Pediatrics
Norma Terrazas, RN
Ellie Wallace, LMSW, Social Work
Sowdhamini Wallace, MD, Emergency Medicine

Additional EBOC Support
Tom Burke, Research Assistant
Sherin Titus, Research Assistant
Karen Gibbs, MSN/MPH, RN, Evidence-Based Practice Specialist
Betsy Lewis, MSN, RN, Evidence-Based Practice Specialist
Jennifer Loveless, MPH, Evidence-Based Practice Specialist
Sheesha Porter, MS, RN, Evidence-Based Practice Specialist
Anne Dykes, MSN, RN, Assistant Director
Kathy Carberry, MPH, RN, Director

No relevant financial or intellectual conflicts to report.

Development Process
This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts
2. Review of Existing External Guidelines
3. Literature Review of Relevant Evidence
   - Searched: Medline, Cochrane, AHRO, Cinahl, Trip, Best BETS, AAP, BMJ Clinical Evidence, Google Scholar
4. Critically Analyze the Evidence
   - Cincinnati Guideline, Emergency Medicine Clinical Policy for Children Younger than Three Years Presenting with Fever, 2 meta-analyses, 42 non-randomized studies, and 4 review articles
5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a FWLS 0-60 Days manual within EBOC.

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. The higher the score, the more comprehensive the guideline.

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. The GRADE criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Type of Evidence</th>
</tr>
</thead>
<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>Quality</td>
<td></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, 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>

Recommendations
Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the management of FWLS in infants 0-60 days. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process
Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children’s Hospital. Content Expert Teams are involved with every review and update.

Disclaimer
Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient’s family, to make the ultimate judgment regarding care.

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## Version History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<td>Mar 2009</td>
<td>Originally completed</td>
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<tr>
<td>Sep 2014</td>
<td>Updated</td>
</tr>
<tr>
<td>Jul 2015</td>
<td>Revision: Literature search on procalcitonin</td>
</tr>
<tr>
<td>Jun 2016</td>
<td>Revision: Antibiotic selection</td>
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<td>Feb 2017</td>
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