**Definition:** An acute febrile illness (temperature ≥100.4°F [38°C]) with uncertain etiology after completion of a thorough history and physical examination. (1-3)

**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. (4,5)

**Inclusion Criteria:**
- Age 0-60 days (Infants ≥35 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 any time during the past 24 hours
- Neonates aged ≤21 days with bronchiolitis
- Neonates and infants (0-60 days) with respiratory viruses including COVID-19

**Exclusion Criteria:**
- History of prematurity with gestational age at birth less than 35 weeks
- Infants aged ≥22 days with bronchiolitis
- 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
- Pneumonia
- Urinary tract infection
- Sepsis/Bacteremia
- Enteritis
- Herpes Simplex Virus (HSV) infection
- Enterovirus
- Parechovirus
- SARS-CoV-2 Virus

**Toxic Criteria** (6,7)
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 (8,9)**

<table>
<thead>
<tr>
<th>Peripheral Pulses</th>
<th>Sign and/or Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary refill</td>
<td>≥ 3 sec</td>
</tr>
<tr>
<td>Skin</td>
<td>Flash (&lt; 1 sec)</td>
</tr>
<tr>
<td>Mental status</td>
<td>Mottled, cool</td>
</tr>
<tr>
<td></td>
<td>Flushed, ruddy, erythoderma (other than face)</td>
</tr>
<tr>
<td></td>
<td>Petechiae below the nipple, any purpura</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systolic BP</th>
</tr>
</thead>
</table>
- Decreased or weak-bound pulses
- Flash (<1 sec)
- Mottled, cool
- Flushed, ruddy, erythoderma (other than face)
- Petechiae below the nipple, any purpura

**Table 2. Vital Sign Changes of Sepsis (8,9)**

<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. (10,11)

Viral pathogens, such as enterovirus, adenovirus, herpes simplex virus, influenza virus, and parainfluenza virus, are also a concern in this patient population. (12,13) There is limited research available on the incidence of SARS-CoV-2 in infants, however preliminary data shows that children, including infants, seem to range from asymptomatic to moderate disease severity. (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. [16,17]

Recommended Laboratory Tests

Infants 0 to 21 Days
- Complete blood count (CBC) with differential and platelets
- Blood culture* (BC) (obtain prior to antibiotic administration)
- Urinalysis (UA) with micro and culture†^ 
- Procalcitonin
- Lumbar puncture (LP)* [gram stain, culture, cell count and diff, glucose, protein, viral culture] ‡
- Enterovirus CSF PCR if pleocytosis present
- HSV testing (blood, CSF, swab specimens, cultures of vesicles) if HSV risk factors present or worsening condition.
- Consider laboratory values of inflammation including procalcitonin and C-reactive protein (CRP)

Infants 22 to 28 Days
- Complete blood count (CBC) with differential and platelets
- Urinalysis with micro and culture†^ 
- Blood culture* (obtain prior to antibiotic administration)
- Procalcitonin
- If inflammatory markers are abnormal, obtain an LP*. Test for gram stain, culture, cell count and diff, glucose, and protein. If pleocytosis present, obtain enterovirus PCR, ‡
- HSV testing (blood, CSF, swab specimens, cultures of vesicles) if HSV risk factors present or worsening condition.

Infants 29 to 60 Days
- Complete blood count (CBC) with differential and platelets
- Urinalysis with micro and culture†^ 
- Blood culture* (obtain prior to antibiotic administration)
- Procalcitonin
- If inflammatory markers are abnormal, consider performing LP*. Test for gram stain, culture, cell count and diff, glucose, and protein. If pleocytosis present, obtain enterovirus PCR, ‡
- HSV testing (blood, CSF, swab specimens, cultures of vesicles) if HSV risk factors present or worsening condition.

Optional Laboratory Testing
- 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)

† Cath (transurethral catheterization) or SPA (suprapubic aspiration)
^ Urine culture and blood culture should be performed prior to antibiotic administration
*LP should be performed prior to antibiotic administration
‡ Tube #1 Glucose, protein
Tube #2 Cell count & diff. Gram stain & culture

Laboratory Test Values

Abnormal Inflammatory Markers
- Procalcitonin >0.5 ng/mL
- ANC <1000 mm³ OR >4000 mm³
* If procalcitonin is not available, may use CRP in combination with elevated temperature as inflammatory markers.

CSF WBC/mm³ Value in Febrile Infants Without Evidence of UTI, IBI, HSV, Enterovirus or Traumatic CSF [18]
- Age 1 – 28 Days
  - Abnormal >18 WBC per mm³
- Age 29 – 60 Days
  - Abnormal >9 WBC per mm³
* Based on absolute white blood cell count. Values not risk stratified. The AAP guideline does not recommend correcting CSF white count or CSF red blood cell count in children with traumatic lumbar punctures.
* Children with traumatic lumbar punctures should follow the branch of the algorithm for uninterpretable CSF.

Herpes Simplex Virus
Evidence shows that there is an increase of the risk of mortality for disseminated HSV with each day of delayed treatment. [19] National guidelines support the consideration of HSV infection as a causative agent for neonates with fever. [20] Laboratory evaluation for neonatal HSV infections should be performed for those with clinical findings suggestive of HSV infection or a maternal history of HSV. [21-24]

HSV Risk Factors [23]
- Maternal primary HSV infection
- Maternal fever
- Vaginal delivery
- Prematurity
- Neonatal seizures
- Vesicular rash
- CSF pleocytosis (monocytosis)
- Elevated hepatic enzymes

Signs/Symptoms of Systemic HSV [24]
- 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. [25]
- Specimens of skin vesicles for HSV culture or PCR
- CSF sample for HSV PCR
- Whole blood sample for HSV PCR
- Swab specimens from the mouth, nasopharynx, conjunctivae, and anus for HSV culture (completed in-hospital) or PCR (currently a send-out lab)
  - To collect swab specimens for culture, the practitioner may utilize one swab for the eye, mouth, nose and rectum in stated order. Different swabs may be used for each specimen location; however, if this method is used the practitioner should put all swabs in the same transport tube.

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Critical Points of Evidence

Evidence Supports

- Complete HSV testing and administer empiric 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. (19,21,25-29) – Strong recommendation, low quality evidence

Remarks: Neonates with age less than or equal to 21 days present a heightened concern for HSV.

- Enterovirus testing (if pleocytosis present) should be utilized in addition to usual care in order to decrease length of stay. (29,30) – 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.”) (31-34) – Strong recommendation, low quality evidence

- The diagnostic work-up for neonatal HSV infection should include all of the laboratory tests listed below. (20)
  - Specimens of skin vesicles for HSV culture or PCR
  - CSF sample for HSV PCR
  - Whole blood sample for HSV PCR
  - Swab specimen from the mouth, nasopharynx, conjunctivae, and anus for HSV culture (completed in-house) or PCR (currently a send-out lab)
  - Remarks: To collect swab specimens for culture, the practitioner may utilize one swab for the eye, mouth, nose and rectum in stated order. Different swabs may be used for each specimen location; however, if this method is used the practitioner should put all swabs in the same transport tube.

Evidence Against

- AST and/or ALT lab tests should not routinely be used for screening for disseminated HSV in all infants 0-28 days with fever. (24,25,35-38) – Strong recommendation, low quality evidence

Recommendations Adopted/Adapted from National Guidelines (39)

Well-Appearing Infants 0-21 Days

- Should assess inflammatory markers.
- Should obtain CSF for analysis (WBC, protein, glucose, Gram stain) and culture for bacteria.
- Should initiate parenteral antimicrobial therapy.
- Clinicians should discontinue parenteral antimicrobial agents and discharge hospitalized patients when all of the following criteria are met: Culture results are negative for 24 to 36 hours or only positive for contaminants; The infant continues to appear clinically well or is improving (e.g., fever, feeding); and There are no other reasons for hospitalization.

Well-Appearing 22-to-28 Day Old Infants

- Should assess inflammatory markers.
- Should obtain CSF for analysis (WBC, protein, glucose, gram stain) and bacterial culture if any inflammatory marker obtained is positive.
- Clinicians should administer parenteral antimicrobial therapy in a hospital if either of the following apply: CSF analysis suggests bacterial meningitis; or Urinalysis result is positive.
- Clinicians may administer parenteral antimicrobial therapy in a hospital if all of the following apply: CSF analysis is normal; Urinalysis is normal; and any IM obtained is abnormal.
- If inflammatory markers and UA are normal, should admit without lumbar puncture and observe off parenteral antibiotic therapy.
  Remarks: If there is a clinical concern, may consider LP and admit on antibiotics.
- Clinicians should discontinue antimicrobial agents and discharge hospitalized infants after 24 to 36 hours of negative culture results if both of the following are met: the infant is clinically well or improving (e.g., fever, feeding); there are no other reasons for hospitalization and there is no other infection requiring treatment (e.g., otitis media).

Well-Appearing 29-to-60 Day Old Infants

- Should assess inflammatory markers.
- May obtain CSF for analysis (WBC, differential, protein, glucose, gram stain), culture for bacteria, and test for enterovirus when CSF pleocytosis is detected if any inflammatory marker is abnormal.
- Need not to obtain CSF for analysis and culture if all inflammatory markers obtained are normal.
- Clinicians should hospitalize infants if CSF analysis, if obtained, is abnormal.
- Clinicians may hospitalize infants if any inflammatory marker obtained is abnormal.
- Clinicians should manage patients at home if all of the following criteria are met:
  - CSF analysis, if CSF obtained, is normal;
  - urinalysis is negative;
  - all IMs obtained are negative;
  - appropriate parental education has been provided;
  - follow-up plans for reevaluation in 24 hours have been developed and are in place; and
  - plans have been developed and are in place in case of change in clinical status, including means of communication between family and providers and access to emergency medical care.
- Clinicians may manage infants without antimicrobial treatment at home without having obtained interpretable CSF if all of the following are met: urinalysis is negative; all IMs obtained are normal; and parents can return promptly if there is a change in infant condition and agree to follow-up in 24 hours. Infants monitored at home should be reassessed in the following 24 hours.

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**Treatment Recommendations** [39]

**Abnormal Inflammatory Markers**
- Procalcitonin >0.5 ng/mL
- ANC <1000 mm$^3$ OR >4000 mm$^3$

*If procalcitonin is not available, may use CRP in combination with elevated temperature as inflammatory markers.*

**Neonates (<21 days)**: (39)
If presenting in clinic setting, refer to EC.
Evaluate with a full sepsis workup and admit to the inpatient area for antibiotic therapy and observation. (20,21,25-28,31,32-34)
Complete HSV testing and administer empiric acyclovir for neonates with no identified bacterial pathogen in CSF and the presence of CSF pleocytosis or uninterpretable CSF and/or exam, concern or possible maternal history of HSV, and/or toxic appearance. (20,21,25-28) Neonates with age less than or equal to 21 days present a heightened concern for HSV.

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 cefTRAZidime should be administered. (40,41)

**Infants 22 to 28 days**: (39)
Assess inflammatory markers. If any inflammatory marker abnormal, obtain an LP. If urine culture positive or CSF indicates bacterial meningitis, administer antibiotics.
Observe all patients in hospital.
Discontinue antibiotics and discharge hospitalized infants after 24 to 36 hours of negative culture results if both of the following are met:
- Clinically well or improving
- No other reasons for hospitalization and/or no other infection requiring treatment

**Infants ≥ 29 days**: (39)
Should assess inflammatory markers.
Need not to obtain CSF for analysis and culture if all inflammatory markers obtained are normal.
Obtain CSF for analysis ([WBC, differential, protein, glucose, gram stain], culture for bacteria, and test for enterovirus when CSF pleocytosis is detected) if any inflammatory marker is abnormal.
Admit infants if CSF analysis, if obtained, is abnormal or uninterpretable.
Manage patients at home if all of the following criteria are met:
- CSF analysis, if CSF obtained, is normal;
- urinalysis is negative;
- all IMs obtained are negative;
- appropriate parental education has been provided;
- follow-up plans for reevaluation in 24 hours have been developed and are in place; and
- plans have been developed and are in place in case of change in clinical status, including means of communication between family and providers and access to emergency medical care.

**Follow-up Care**
Healthcare provider to follow up on blood and urine cultures (if discharged before 48 hours). Urine and CSF cultures are not automatically read.
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
- Reliable phone and transportation
- Parent willingness to observe and communicate changes in condition
- Reliable follow-up available 12-24 hours post-discharge
- Caregiver and PCP agree with plan
- Caregiver understands discharge education

**Differences from AAP Guideline**
The American Academy of Pediatrics (AAP) Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old guideline was contextualized to the requirements of patients within Texas Children’s Hospital. Due to the concern of distinguishing bronchiolitis from upper respiratory tract infections as well as the risk of a potential untreated SBI, patients with bronchiolitis 21 days or less are included within this guideline. Patients born at 35 weeks gestational age are included within the guideline to provide a standardized treatment path. The gestational age of 35 weeks aligns with care in the newborn nursery as opposed to needing NICU level care. Patients 22-to-28 days old will be observed in the hospital due to the risk of an untreated SBI in our population of patients that includes a large proportion without access to reliable follow-up or a primary care physician. The decision to list procalcitonin and ANC as inflammatory markers was due to availability of procalcitonin at TCH campuses and the better diagnostic accuracy to detect bacterial infection compared to other inflammatory markers. The cut-off value for ANC was adapted locally and a minimum cut-off was added to ensure evaluation for neutropenia. Evidence regarding the diagnostic accuracy of procalcitonin and ANC cut-off values can be found within the AAP Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old Guideline.

**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 (42)
Consider insurance/Medicaid formulary restrictions
Infants 0 - 21 Days for ≥35 Weeks Gestational Age (GA)

<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>
<tr>
<td>Ampicillin</td>
<td>≤7 days: 100 mg/kg/DOSE every 8 hours</td>
</tr>
<tr>
<td></td>
<td>&gt;7 days:</td>
</tr>
<tr>
<td></td>
<td><strong>GA 35-43 weeks</strong>: 50 mg/kg/DOSE every 8 hours</td>
</tr>
<tr>
<td></td>
<td><strong>GA ≥44 weeks</strong>: 50 mg/kg/DOSE every 6 hours</td>
</tr>
<tr>
<td></td>
<td>If concern for meningitis: 75 mg/kg/DOSE every 6 hours</td>
</tr>
<tr>
<td>Gentamicin Sulfate</td>
<td>Neotanes:</td>
</tr>
<tr>
<td></td>
<td>PNA ≤7 days: 4 mg/kg/DOSE every 24 hours</td>
</tr>
<tr>
<td></td>
<td>PNA &gt;7 days: 5 mg/kg/DOSE every 24 hours</td>
</tr>
<tr>
<td><strong>Use in lieu of gentamicin for suspected meningitis or CSF pleocytosis</strong></td>
<td></td>
</tr>
<tr>
<td>CefTRIAzide</td>
<td>Neonates 0-28 days: 50 mg/kg/DOSE every 8 hours</td>
</tr>
<tr>
<td><strong>Treatment of choice for suspected Staphylococcus</strong></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>&lt;7 days old:</td>
</tr>
<tr>
<td></td>
<td>&gt;2 kg: 10 to 15 mg/kg/DOSE every 8 to 12 hours</td>
</tr>
<tr>
<td></td>
<td>≥7 to 28 days:</td>
</tr>
<tr>
<td></td>
<td>&gt;2 kg: 10 to 15 mg/kg/DOSE every 6 to 8 hours</td>
</tr>
<tr>
<td><strong>Treatment of choice for Herpes Simplex Virus (HSV)</strong></td>
<td></td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Neonates and Infants: 20 mg/kg/DOSE every 8 hours</td>
</tr>
</tbody>
</table>

Infants 22 – 28 Days

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Empirical Therapy (IM/IV)</strong></td>
<td></td>
</tr>
<tr>
<td>CefTRIAXone</td>
<td>50 mg/kg/DOSE once</td>
</tr>
<tr>
<td><strong>Treatment for Suspected Bacterial Meningitis (IV)</strong></td>
<td></td>
</tr>
<tr>
<td>Ampicillin†</td>
<td>*Meningitis or other severe infection, IV: 75 mg/kg/DOSE every 6 hours</td>
</tr>
<tr>
<td>CefTRIAXone†</td>
<td>Infants 22-28 days:</td>
</tr>
<tr>
<td></td>
<td>*Meningitis, IV: 100 mg/kg/DOSE every 24 hours</td>
</tr>
<tr>
<td></td>
<td><strong>NOTE</strong>: Not for use in patients receiving Y-site administration of calcium-containing IV fluids with a single lumen or single IV site</td>
</tr>
<tr>
<td><strong>Treatment of choice for suspected Staphylococcus†</strong></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15 mg/kg/dose every 8 hours</td>
</tr>
</tbody>
</table>

Infants 29 – 60 Days

<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>Treatment for Suspected Bacterial Meningitis (IV)</strong></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Infants &gt;28 days and children: 15 mg/kg/dose every 8 hours</td>
</tr>
<tr>
<td>CefTRIAXone†</td>
<td>Infants &gt;28 days:</td>
</tr>
<tr>
<td></td>
<td>*Meningitis, IV: 100 mg/kg/DOSE every 24 hours</td>
</tr>
<tr>
<td></td>
<td><strong>NOTE</strong>: Not for use in patients receiving Y-site administration of calcium-containing IV fluids with a single lumen or single IV site</td>
</tr>
<tr>
<td><strong>Treatment of choice for suspected Staphylococcus†</strong></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15 mg/kg/dose every 8 hours</td>
</tr>
</tbody>
</table>

†Reduce antibiotics to general dosing for suspected infection once meningitis ruled out.
*For all age groups, consult ID for patients with enteroviral negative meningitis.
TCH Evidence-Based Outcomes Center Clinical Algorithm

Neonates & Infants with Fever Without Localizing Signs (FWLS) 0 - 21 days

Clinical standards are developed for 80% of the patient population with a particular disease. Each practitioner must use his/her clinical judgment in the management of any specific patient.

**Exclusion Criteria:**
- Gestational age <35 weeks
- 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

*Note: Positive viral test including COVID-19 and/or a diagnosis of bronchiolitis are NOT exclusions for initiation of age-specific work-ups.*

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**Algorithm**

1. **Begin**
   - Fever ≥ 100.4°F (38°C)
   - NO
   - Well appearing with NO source of infection
   - YES
   - OFF algorithm
     Manage as appropriate to clinical findings

2. If pleocytosis (WBC >18/mm³) or uninterpretable CSF
   (Bacterial Meningitis Score should NOT be used in this population)
   - Admit patient
     - Administer ceftazidime (meningitis dosing) in lieu of gentamicin for antibiotics
     - Administer Acyclovir and send recommended HSV labs if not already done (see below)
     - Add enterovirus CSF PCR if sample available

3. Enterovirus CSF PCR
   - Positive
     - Consider ID consult for enteroviral negative meningitis OFF Algorithm
     Manage as appropriate for clinical findings
   - NO

4. Recommended HSV Labs:
   - HSV PCR from CSF and blood
   - Swab specimens from mouth, nasopharynx, conjunctiva, and anus for HSV culture (competed in-hospital) or PCR (currently a send-out lab)
   - Specimens of skin vesicles if present for PCR
   Further Instructions: To collect swab specimens for culture, the practitioner may utilize one swab for the eye, mouth, nose and rectum in stated order. Different swabs may be used for each specimen location; however, if this method is used the practitioner should put all swabs in the same transport tube.

---

**HSV Testing Orders**
- Blood – HSV 1&2 Real Time PCR, Blood (LABHSVVDNA)
- CSF – HSV 1&2 Real Time PCR, CSF (LABHSV2)
- Lesion PCR – HSV and VZV by PCR (LABHSVVZV)
- Lesion culture – Viral Culture HSV (LABHSVVCX)
- Surface surveillance culture (eye, nose, mouth, rectal) – Viral Culture HSV Surveillance (LABHSVSRV)
- Surface surveillance PCR (eye, nose, mouth, rectal) – Herpes Simplex Virus 1 & 2 (HSV-1 & HSV-2), By Quantitative Real-Time PCR, Skin Swab (LABHSVPS)

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TCH Evidence-Based Outcomes Center Clinical Algorithm
Infants with Fever Without Localizing Signs (FWLS) 22 - 28 days

Clinical standards are developed for 80% of the patient population with a particular disease. Each practitioner must use his/her clinical judgment in the management of any specific patient.

Begin

- Fever ≥ 100.4°F (38°C)
- Well appearing with NO source of infection

OFF algorithm
Manage as appropriate to clinical findings

Perform LP

- Any Abnormal Inflammatory Marker? Procalcitonin^ >0.5 ng/mL?

May perform LP

- May administer parenteral antimicrobials
  - If UA positive, administer ceftriaxone

LP Performed?

- CSF Pleocytosis (>18 WBC/mm³) or Uninterpretable?

Administer parenteral antimicrobials
- If concerned about HSV, add acyclovir and send recommended HSV labs (see below)
  - Add enterovirus CSF PCR
  - Observe in hospital

Pathogen or source identified?

Treat Infection
- If Concern for bacterial meningitis, administer cefazidine in lieu of gentamicin for antibiotics (Bacterial Meningitis Score should NOT be used in this population)
- Consult ID for patients with enteroviral negative meningitis

Recommended HSV Labs:
- HSV PCR from CSF and blood
- Swab specimens from mouth, nasopharynx, conjunctiva, and anus for HSV culture (competed in-hospital) or PCR (currently a send-out lab)
- Specimens of skin vesicles if present for PCR

Further Instructions: To collect swab specimens for culture, the practitioner may utilize one swab for the eye, mouth, nose and rectum in stated order. Different swabs may be used for each specimen location; however, if this method is used the practitioner should put all swabs in the same transport tube.

H SV Testing Orders
- Blood – HSV 1&2 Real Time PCR, Blood (LABHSVSDNA)
- CSF – HSV 1&2 Real Time PCR, CSF (LAB1230056)
- Lesion PCR – HSV and VZV by PCR (LABVZHSV)
- Lesion culture – Viral Culture HSV (LABHSVVCX)
- Surface surveillance culture (eye, nose, mouth, rectal) – Viral Culture HSV Surveillance (LABHSVSRV)
- Surface surveillance PCR (eye, nose, mouth, rectal) – Herpes Simplex Virus 1 & 2 (HSV-1 & HSV-2), By Quantitative Real Time PCR, Skin Swab (LABHSVPPP)

Urine and CSF cultures are not automatically read. Call lab (x45152) prior to discharge for results.

*Procalcitonin has the highest diagnostic accuracy to differentiate between viral and invasive bacterial infection (18).

*Complete HSV testing and administer empiric 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.

Exclusion Criteria

- Positive viral test including COVID-19 is NOT an exclusion for initiation of age specific antimicrobials.
- To collect swab specimens for culture, the practitioner should put all swabs in the same transport tube.
- Swabs may be used for each specimen location; however, if this method is used the practitioner should put all swabs in the same transport tube.

Gestational age <35 weeks
- Underlying conditions that affect immunity or may otherwise increase risk of Serious Bacterial Infection
- Toxic/Septic in appearance
- Bronchoitis
- Currently receiving a for FWLS
- Received routine immunizations within 48 hours of presentation
- Presents with seizures
- Requires ICU management
- Has an identified focus of infection

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Texas Children’s Hospital
TCH Evidence-Based Outcomes Center Clinical Algorithm
Infants with Fever Without Localizing Signs (FWLS) 29 - 60 days

Clinical standards are developed for 80% of the patient population with a particular disease. Each practitioner must use his/her clinical judgment in the management of any specific patient.

Begin
- Fever ≥ 100.4°F (38°C)
  - Yes
  - OFF algorithm: Manage as appropriate to clinical findings
  - No
- Well appearing with NO source of infection
  - Yes
  - OFF algorithm: Manage as appropriate to clinical findings
  - No

Normal inflammatory markers

Positive Urinalysis?
- Yes
- Administer antibiotics
- Admit patient
- May observe closely in hospital or at home

Patient eligible for discharge once criteria met?
- Yes
- Treat per UTI Guideline
- Pathogen or source identified at 24 to 36 hours?
  - Yes
  - Discontinue antibiotics if ordered
  - Discharge hospitalized infants if meeting discharge milestones
  - No
  - Administer antibiotics
  - Admit patient

Negative Urinalysis?
- Yes
- Administer antibiotics
- Admit patient
- May observe closely in hospital or at home
- Pathogen or source identified at 24 to 36 hours?
  - Yes
  - Discontinue antibiotics if ordered
  - Discharge hospitalized infants if meeting discharge milestones
  - No
  - Administer antibiotics
  - Admit patient

Recommended HSV Labs:
- HSV PCR from CSF and blood
- Swab specimens from mouth, nasopharynx, conjunctiva, and anus for HSV culture (competing in-hospital) or PCR (currently a send-out lab)
- Specimens of skin vesicles if present for PCR

Further Instructions: To collect swab specimens for culture, the practitioner may utilize one swab for the eye, mouth, nose and rectum in stated order. Different swabs may be used for each specimen location; however, if this method is used the practitioner should put all swabs in the same transport tube.

Septic Shock Criteria
- Gestational age <35 weeks
- Underlying conditions that affect immunity or may otherwise increase risk of Serious Bacterial Infection
- Toxic/Sepsis in appearance
- Current receiving antibiotics for FWLS
- Received routine immunizations within 48 hours of presentation
- Presents with seurses
- Requires ICU management
- Has an identified focus of infection

*Note: Positive viral test including COVID-19 is NOT an exclusion for initiation of age specific work-up.

Urine and CSF cultures are not automatically read. Call lab (45152) prior to discharge for results.
References


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.

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Sheesha Porter, MSN, RN, Evidence-Based Practice Specialist
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The following financial and/or intellectual conflict(s) was/were identified and addressed to ensure objectivity: Content Expert Team member A. Cruz, MD is the author of research on clinical decision rules and management of HSV.

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
   - Management of Infants 0-60 Days with Fever of Unknown Source, Cincinnati Children’s Hospital; Neonatal Fever, Seattle Children’s Hospital; Evaluation/Treatment of Febrile Young Infants (0-56 Days), Children’s Hospital of Philadelphia; Red Book – Report of Committee of Infectious Disease, American Academy of Pediatrics
3. Literature Review of Relevant Evidence
   - Searched: Medline, Cochrane, Cinahl, AAP, BMJ Clinical Evidence, Google Scholar
4. Critically Analyze the Evidence
   - 2 meta-analyses, 41 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 electronic 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>Quality</th>
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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>
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</table>

<table>
<thead>
<tr>
<th>Type of Evidence</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
<th>Very Low</th>
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<tbody>
<tr>
<td>Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies</td>
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<tr>
<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>
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<tr>
<td>Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence</td>
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<td></td>
<td></td>
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<tr>
<td>Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence</td>
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</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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April 2022
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<th>Date</th>
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<tr>
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<tr>
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<tr>
<td>July 2023</td>
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