



Clinical Practice Guidelines for Febrile Infants

Objective:

The purpose of this Febrile Infant Clinical Practice Guideline is to standardize care of the febrile with the goal of improving patient outcomes.

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

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

Definition:

Fever in infants 7 to 60 days of life is elevation of central temperature to 38.0°C or higher.

Target Users:

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

Guideline Inclusion Criteria:

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

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

Guideline Exclusion Criteria:

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

Clinical Questions Answered by this Guideline:

1. What criteria can be used to determine if a febrile infant 7-60 days of age is at low risk for a bacterial infection?
2. When should HSV testing be performed and treatment initiated in a febrile infant 7 to 60 days of age?
3. What empiric antimicrobials are recommended in the febrile infant 7 to 60 days of age?

Differential Diagnosis:

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

Practice Recommendations:

- Assessing fever in infant

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

Management of Ill Appearing Febrile Infants 7 to 60 Days

Full Sepsis Evaluation of Ill Appearing Infants

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

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

A full sepsis evaluation includes the following:

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

These infants should undergo a Herpes Simplex Virus (HSV) Risk Assessment with the HSV Checklist (discussed later on page 6) and be managed accordingly.

Inpatient Management

- All ill appearing infants are to be admitted to the hospital

- Empiric administration of IV antibiotics (+/- acyclovir depending on HSV risk) is required. Drug dosing and frequency is listed below.

Age	Suggested Empiric Antibiotics	High risk for HSV
Infants 7-28 days	1. Ampicillin 75 mg/kg IV q 6 hrs 2. Cefotaxime* 50 mg/kg IV q 6 hrs OR Gentamicin 4 mg/kg IV q 24 hrs <small>(* may substitute cefepime 50 mg/kg IV q 8 hrs if cefotaxime shortage)</small>	Acyclovir 20 mg/kg IV q 8 hrs
Infants 29-60 days	1. Ampicillin 75 mg/kg IV q 6 hrs 2. Ceftriaxone 50 mg/kg IV q 12 hrs Recommend adding vancomycin 15 mg/kg IV q 6 hrs if CSF findings suggestive of meningitis	

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

Management of Well Appearing Febrile Infants 7 to 60 Days

Identification of infants at risk for bacterial infections: The Bacterial Risk Assessment

The Bacterial Risk Assessment is based on the Rochester Criteria to further stratify which infants are at high risk for a bacterial cause of their fever. This assessment uses both the patient's history as well as some laboratory values taken at the time of evaluation to stratify risk.

All infants evaluated for fever should have the following initial screening tests:

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

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

Low Risk Febrile Infant

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

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

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

Management of Low Risk Febrile Infants 7 to 28 Days

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

- Blood and urine cultures are assessed until final results are available. Any positive cultures judged not to be a contaminant at any time requires the infant to undergo a lumbar puncture and antibiotic administration.
- Low risk patients eligible for discharge after 24 hours if remain well appearing and blood and urine cultures remain negative. To note, urine culture is only evaluated once per day by laboratory protocol. Urine culture results should be verified prior to discharge.
- If there is a *clinical decision to administer antibiotics* in this patient population, a lumbar puncture should be performed. If performing a lumbar puncture the following should be obtained.
 1. Cerebral spinal fluid (CSF) cell count with differential, protein, and glucose (Obtain concurrent serum glucose if not recently obtained).
 2. CSF meningitis/encephalitis panel (includes gram stain and bacterial culture)
- These infants should undergo a Herpes Simplex Virus (HSV) Risk Assessment with the HSV Checklist (discussed later on page 6).
- Empiric administration of IV antibiotics (+/- acyclovir depending on HSV risk) is required. Drug dosing and frequency is listed below.

Age	Suggested Empiric Antibiotics	High risk for HSV
Infants 7-28 days	1. Ampicillin 75 mg/kg IV q 6 hrs 2. Cefotaxime* 50 mg/kg IV q 6 hrs OR Gentamicin 4 mg/kg IV q 24 hrs (* may substitute cefepime 50 mg/kg IV q 8 hrs if cefotaxime shortage)	Acyclovir 20 mg/kg IV q 8 hrs

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

Management of Low Risk Febrile Infants 29 to 60 Days

Infants at low risk for bacterial infection in this age group may be considered *candidates for care at home* depending on caregivers' ability and follow up is assessed and judged to be reliable. This is determined by the Ambulatory Discharge Disposition Checklist.

- Blood and urine cultures are assessed until final results are available. Any positive cultures judged not to be a contaminant at any time requires the infant to be cared for in the hospital.
- Alternatively, the infant can be admitted to the hospital for *observation without administration of antibiotics* until culture results can be assessed (at minimum 24 hours)
- Low risk patients who were admitted are eligible for discharge at 24 hours if remains well appearing and blood and urine cultures remain negative. To note, urine culture is only evaluated once per day by laboratory protocol. Urine culture results should be verified prior to discharge.
- If there is a *clinical decision to administer antibiotics* in this patient population, a lumbar puncture should be performed. Administration of antibiotics requires hospital admission. If performing a lumbar puncture the following should be obtained.
 1. Cerebral spinal fluid (CSF) cell count with differential, protein, and glucose (Obtain concurrent serum glucose if not recently obtained).
 2. CSF meningitis/encephalitis panel (includes gram stain and bacterial culture)
- These infants should undergo a Herpes Simplex Virus (HSV) Risk Assessment with the HSV Checklist (discussed later on page 6).
- Empiric administration of IV antibiotics (+/- acyclovir depending on HSV risk) is required. Drug dosing and frequency is listed below.

Age	Suggested Empiric Antibiotics	High risk for HSV
Infants 29-60 days	1. Ampicillin 75 mg/kg IV q 6 hrs 2. Ceftriaxone 50 mg/kg IV q 12 hrs Recommend adding vancomycin 15 mg/kg IV q 6 hrs if CSF findings suggestive of meningitis	Acyclovir 20 mg/kg IV q 8 hrs

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

Management of High Risk Infants 7-60 days

- A lumbar puncture should be performed for all high risk infants. If performing a lumbar puncture the following should be obtained.
 1. Cerebral spinal fluid (CSF) cell count with differential, protein, and glucose (Obtain concurrent serum glucose if not recently obtained).
 2. CSF meningitis/encephalitis panel (includes gram stain and bacterial culture)
- These infants require hospital admission.
- These infants should undergo a Herpes Simplex Virus (HSV) Risk Assessment (discussed later on page 6).
- Empiric administration of IV antibiotics (+/- acyclovir depending on HSV risk) is required. Drug dosing and frequency is listed below.

Age	Suggested Empiric Antibiotics	High risk for HSV
Infants 7-28 days	1. Ampicillin 75 mg/kg IV q 6 hrs 2. Cefotaxime* 50 mg/kg IV q 6 hrs OR Gentamicin 4 mg/kg IV q24 hrs <small>(* may substitute cefepime 50 mg/kg IV q 8 hrs if cefotaxime shortage)</small>	Acyclovir 20 mg/kg IV q 8 hrs
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- Antipyretic administration: Acetaminophen may be administered (10-15 mg/kg/dose every 4-6 hours [Max 75 mg/kg/day]) PO or PR for infants with fever when assessed to be uncomfortable.
- Treatment of an infant with a positive blood, urine, or CSF culture is dependent on the infection site and the pathogen identified.
- Patient would be eligible for discharge at 36 hours if remains well appearing and blood, urine, CSF cultures, and HSV PCRs (if sent) remain negative. To note, urine culture is only evaluated once per day by laboratory protocol. Urine culture results should be verified prior to discharge.

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

Epidemiology

1. The prevalence of HSV infection is low: 0.3% in neonates with fever and 1.0% in neonates with fever and CSF pleocytosis (Caviness, Demmler et al. 2008) or 5.1 cases per 100,000 live births (Mahnert, Roberts et al. 2007).
2. Mortality and morbidity for untreated neonatal HSV disease is high.

3. HSV can manifest as (RedBook 2015)
 - a. Disease localized to the skin, eye, and/or mouth (SEM disease): 45% of cases
 - b. Localized CNS disease, with or without skin involvement (CNS disease): 30% of cases
 - c. Disseminated disease involving multiple organs, most prominently liver and lungs (also present in 60% to 75% of cases also involving the CNS): 25% of cases

HSV Risk Factors

Infants 7 to 60 days of life are recommended for HSV testing if they present with any of the following:

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

Diagnostic Testing for HSV High Risk Infants

The following diagnostic tests are recommended *in addition* to the full diagnostic work up for febrile infants as described above:

- Verification that the CSF meningitis/encephalitis panel has been sent (includes HSV CSF PCR)
- HSV surface (mouth, nasopharynx, conjunctivae, rectum) and vesicle swabs for PCR
- HSV blood PCR

Inpatient Management for High Risk HSV Infants

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

Guideline Preparation:

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

Results of this study are reviewed in “Reducing Variability in the Infant Sepsis Evaluation (REVISE): A National Quality Initiative,” (Biondi EA, et al. *Pediatrics*. Aug. 21, 2019, <https://doi.org/10.1542/peds.2018-2201>).

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