

Fever in infants ages 8 to 60 days: An updated guideline for evaluation

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ABSTRACT

Fever in infants under age 60 days is a leading cause of ED, urgent care, and primary care visits. Most infants present as well-appearing, and guidelines for the workup and appropriate management of these children have varied over the decades. Additionally, testing availability, accuracy, and changing bacterial prevalence patterns have rendered many guidelines obsolete. An updated guideline from the American Academy of Pediatrics provides a foundation for clinician evaluation of patients in this vulnerable age group.

Keywords: fever, pediatrics, neonatal, infant, guideline, American Academy of Pediatrics

Learning objectives

- Summarize the prevalence of pediatric fever presentation.
- Describe how to recognize a well-appearing infant.
- Describe the differential for a febrile, well-appearing infant.
- Identify the workup for febrile, well-appearing infants ages 8 to 60 days.

Fever is one of the most frequent reasons that parents and caregivers seek medical evaluation for their children. In fact, about 14 out of every 1,000 healthy babies born full-term develop a fever between ages 8 to 60 days, according to the American Academy of Pediatrics (AAP).¹ In 2019, infants had the highest rate of ED visits at 123 visits per 100 people, and nearly 14% of all US children visited urgent care.^{2,3} Pediatric fever accounted for about 20% of these emergency visits.⁴ Pediatric fevers can present secondary to infection, immunization, inflammatory processes, neurologic illnesses, thyrotoxicosis, genetic syndromes, drug intoxication, or malignancy.⁴ Because of the broad differential diagnosis of early-life fever of unknown origin, workup strategies have largely varied. Attempts to develop evidence-

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based approaches and prediction models to guide the evaluation and management of young infants with fever are not new, with efforts spanning the past 40 years.⁵ Despite these attempts, evidence reveals that these recommendations have not been routinely followed in primary care or acute care settings.^{6,7} Additionally, factors such as prenatal group B streptococcal testing and immunizations leading to changing bacterial patterns, advancements in laboratory availability and accuracy, and the desire to limit unnecessary testing and costs to parents have necessitated a standardized approach for clinician guidance. Because of the varying approaches observed in managing young infants with fever, the need for an evidence-based guideline from an authority with broad representation was recognized. In 2021, the AAP undertook the development of an authoritative guideline with help from the Agency for Healthcare Research and Quality that supported the evidence review.¹ The AAP guideline focuses on evaluating and treating well-appearing infants presenting to the clinic with a fever of unknown origin. This article reviews and summarizes the AAP recommendations for evaluating this select population.

WHAT IS A WELL-APPEARING CHILD?

The AAP guideline applies to well-appearing infants ages 8 to 60 days who have documented rectal temperatures of 38° C (100.4° F) or greater at home in the past 24 hours or determined in a clinical setting, had a gestation between 37 and 42 weeks, and are at home after discharge from a newborn nursery or were born at home.¹ Important exclusion criteria include infants born before 37 weeks' gestation; under age 2

Key points

- Febrile infants account for a large number of pediatric evaluations.
- Infants ages 8 to 60 days have a broad differential for fever of unknown origin and warrant more aggressive initial evaluation.
- When evaluating a febrile infant, consider these recommendations as well as parental preferences through shared decision-making.

weeks with complicated maternal courses (such as maternal fever, infection, and/or anti-infective use); those with a high suspicion for herpes simplex virus (HSV) infection (for example, vesicles), evident focal infections, clinical bronchitis, immunocompromise, neonatal history of surgery or previous infection, or presence of congenital or chromosomal abnormalities; medically fragile infants who need technologic intervention to live; and infants who have received immunizations within the last 48 hours.¹ The guideline is intended for infants without an obvious source of infection and should not be used if the infant is not well-appearing or if the clinician is uncertain as to whether the infant is well-appearing. The AAP recommendations for workup for well-appearing febrile infants based on age follow.

INFANTS AGES 8 TO 21 DAYS

- **Urinalysis** is recommended.¹ *Escherichia coli* has surpassed group B *Streptococcus* as the leading cause of bacteremia in infants ages 8 to 60 days.⁸ Upwards of 10% of febrile infants have a urinary tract infection (UTI) as an underlying source of infection.⁹ Therefore, AAP recommends clinicians obtain a urine specimen via a catheter or suprapubic aspiration and order a culture if the urinalysis is positive.¹ For this guideline, urinalysis is considered positive if it contains leukocyte esterase or more than 5 white blood cells (WBCs) per high-powered field in centrifuged urine, or more than 10 WBCs/mm³ in uncentrifuged urine on microscopy using a hemocytometer.¹

Ninety-four percent of patients with UTI have leukocyte esterase in the urine and 97% to 100% have positive leukocyte esterase with coexisting bacteremia.⁹ The 2016 AAP recommendations defined UTI as pyuria and 50,000 colony-forming units (CFUs) on appropriately collected specimen.¹⁰ However, further recommendations include the consideration of 10,000 CFUs in catheterized specimens with coexisting pyuria and fevers as positive specimens.⁹ Urine specimens obtained through alternative methods than those listed above have been shown to have a high false-positive rate and should not be used.¹¹

- **Blood cultures** are recommended.¹ In one study in the United Kingdom, 53,276 blood cultures reviewed over a span of 8 years showed a 2.5% positivity rate, a significant rate of potential bacteremia.¹² In this same study, 92% of pathogens in the same 2.5% of positive blood cultures were identified at the 24-hour mark.¹² The AAP recom-

mends admitting febrile infants ages 8 to 21 days to the hospital for treatment.¹ Blood cultures assist with earlier detection of bacteremia and are not intended to alter the care plan at the point of service.¹

- **Lumbar puncture** is recommended.¹ Obtain a cerebrospinal fluid (CSF) sample for WBC count, protein, glucose, Gram stain, bacterial culture, and, if the patient is at increased risk, HSV testing.¹ In addition to the observation of vesicles and/or seizures, infants should be classified at risk for HSV if they have any of the following: maternal history of genital HSV lesions within 48 hours of giving birth or up to 48 hours after giving birth, presence of mucous membrane ulcerative lesions, hypothermia, leukopenia, thrombocytopenia, elevated alanine aminotransferase (ALT), and pleocytosis with a negative Gram stain on CSF.¹ Studies show a prevalence of 2 to 5 per 100,000 children with HSV infection.¹ These children may present with nonspecific features such as fever, poor appetite, and lethargy.¹³ Group B *Streptococcus* remains a common source of infection and should be on the differential.⁸ Consider further testing of CSF samples for enterovirus during the summer months or if the specimen has pleocytosis.¹⁴ Consider regional enterovirus patterns when determining whether to test CSF regardless of pleocytosis.¹

The AAP recommends lumbar puncture in all febrile, well-appearing infants ages 8 to 21 days old but notes that lumbar puncture is not always successful.¹ The rate of failure and/or traumatic lumbar puncture in infants younger than age 90 days is 20% to 50%.¹⁵ Additionally, 25% to 40% of lumbar punctures are dry punctures and 10% to 30% are bloody punctures.¹⁵ One multicenter study showed that only 13% of lumbar punctures indicated a pathogenic source of the identified bacteria, and 87% proved to be contaminated samples.¹⁶ Clinicians may consider the use of ultrasonography to assist in obtaining CSF.¹⁷

- **Inflammatory markers** should be considered, but no single inflammatory marker is reliable for risk stratification.¹ Consider elevations in temperature (greater than 38.5° C), WBC count and components, C-reactive protein (CRP), and procalcitonin. The AAP recommends that clinicians consider inflammatory markers in children ages 8 to 21 days.¹ The primary benefit of inflammatory markers is their influence in determining cessation of care during the hospital stay.¹ The use of inflammatory markers may not be necessary or appropriate in all cases in the emergency or urgent setting—the results would not alter treatment or disposition planning because AAP recommends admission for all febrile children ages 8 to 21 days.

INFANTS AGES 22 TO 28 DAYS

The risk of bacteremia and bacterial meningitis is lower in infants ages 22 to 28 days compared with those ages 8 to 21 days.¹ However, studies have shown that infants ages 22 to 28 days still have higher risk than older infants.¹

Therefore, the workup of this age group was separated from the 8-to-21-days age range because of differences in their age-based risk stratifications.

- **Urinalysis** is recommended and should be performed via catheterization or suprapubic aspiration and, if positive, cultured.¹ If the urine specimen is obtained by bag, spontaneous void, or stimulated void and results are positive, collect a repeat specimen via catheterization or suprapubic aspiration, and if it is positive, obtain a culture.¹

- **Blood cultures** are recommended.¹ A study of 449 neonates in Israel assessed rates of serious bacterial infections in the first 4 weeks of life and found 87 cases of serious bacterial infections; 12.1% were in infants ages 22 to 28 days.¹⁸ This shows that although infants ages 22 to 28 days are at a lower risk of serious bacterial infection than younger infants, the risk still is significant. Therefore, AAP recommends blood cultures in all febrile, well-appearing infants ages 22 to 28 days.

- **Inflammatory markers** are recommended.¹ Despite no evidence showing that any one inflammatory marker is sufficient for risk stratification, all current pediatric fever guidelines incorporate inflammatory markers into their algorithms.¹ For infants with negative urinalysis and/or pending culture results, inflammatory markers can help guide whether to initiate antimicrobial therapy.¹

Temperature is the most readily available inflammatory marker. A Pediatric Research in Office Settings Network study of 63 cases of serious bacterial infections found that a temperature greater than 38.5° C when combined with an ill appearance and age less than 25 days had a sensitivity of 93.7% and a negative predictive value of 99.6% for infection.⁶ In another study, the addition of a high-risk temperature criterion (temperature greater than 38.5° C) to the Rochester Criteria for Febrile Infants increased sensitivity to 96.7%.¹⁹ However, as an independent predictor, 30% of febrile infants with serious bacterial infections have maximum documented fevers of 38.5° C or lower, making the use of temperature alone as a predictor unreliable.²⁰

WBC count and absolute neutrophil count (ANC) serve as additional inflammatory markers that are assistive; however, research has shown neither is sufficient as a standalone test and a normal WBC count has no reassuring properties to the workup of a febrile infant.²¹

CRP is more accurate than WBC count or ANC in patients with bacteremia or meningitis.²²

Procalcitonin remains the best independent predictor of serious bacterial infections.²² Procalcitonin has been shown to increase quickly and early in patients with infection and is more specific for bacterial infection than other inflammatory markers.^{1,22} However, despite being the best independent inflammatory marker, procalcitonin may remain negative in early illness and should not be used as a sole test to rule out serious bacterial infection.^{23,24}

- **Lumbar puncture** should be considered in hospitalized infants and those with pending blood and urine cultures.

Consider lumbar puncture regardless of urinalysis results and even if the patient had no abnormal inflammatory markers.¹ If any inflammatory marker is abnormal, CSF analysis is recommended.

INFANTS AGES 29 TO 60 DAYS

- **Urinalysis** is recommended and should be obtained by bag, spontaneous void, or stimulated void; if positive, obtain a catheterization or suprapubic aspiration specimen for culture.¹ Exceptions to the recommendation for urinalysis are circumcised males, who have shown an overall risk of UTI of less than 1%.²⁵ One study showed an overall 50% decrease in painful catheterization, no increased length of stay, and no missed instances of UTI, despite limiting cultures to only infants with positive urinalysis via other means.²⁶ Specimens collected outside of catheterization or suprapubic aspiration are not appropriate for culture because of a high contamination rate.¹¹

- **Blood cultures** are recommended.¹ Rates of serious bacterial infections continue to diminish with every week of age but remain at just under 2% and warrant a blood culture for this age group.

- **Inflammatory markers** are recommended.¹ Statistics about the use of inflammatory markers and their ability to be used as sole tests for risk stratification remain the same as discussed for younger infants. In infants ages 29 to 60 days, for whom hospitalization is not a strict recommendation, inflammatory markers may assist in the decision to start antimicrobial therapy in children with negative urinalysis, pending urinalysis, pending blood cultures, or pending CSF analysis.¹ Additionally, inflammatory markers may assist with disposition decisions in the setting of a negative, bloody, or failed lumbar puncture.¹

- **Lumbar puncture** should be considered.¹ In infants ages 29 to 60 days, the decision to perform a lumbar puncture depends on inflammatory marker results. Inflammatory markers are predictive of serious bacterial infection, including bacterial meningitis. For well-appearing infants ages 29 to 60 days, the rates of meningitis in published reports are low (64 cases out of more than 25,000 febrile infants, or 0.25%) but data are lacking to compare the prevalence of positive versus negative inflammatory markers in this population.^{1,27} The use of inflammatory markers has increased predictive model sensitivity to greater than 90%.¹ Therefore, any positive inflammatory marker based on current evidence warrants a more thorough workup of the child, including lumbar puncture consideration. However, if all inflammatory markers are normal, no CSF analysis is necessary. Given the high sensitivity of inflammatory markers and the low rates of bacterial meningitis in infants ages 29 to 60 days, more than 4,000 lumbar punctures would be necessary to avoid one delayed case of serious bacterial infection. The AAP does not consider a positive urinalysis alone to be an indicator of a need for lumbar puncture.

CONCLUSION

Pediatric visits to the ED, urgent care, and primary care can be stressful for clinicians, distressing to parents, and cause difficulty in decision-making as clinicians attempt to avoid unnecessary testing and patient discomfort. These concerns have led to a variety of evaluative approaches across clinical settings. Because infants ages 8 to 60 days remain at high risk of serious bacterial infection, a more consistent, evidence-based approach to fever in a well-appearing infant is warranted. Treatment and disposition guidance also are covered by the AAP in this guideline, though not reviewed here.¹

Difficulties with the current guideline include the lack of evidence about rapid respiratory viral swabs. No recommendation exists for whether a positive viral swab alters the above testing recommendations; further study is warranted to determine rates of coexisting positive respiratory illness and serious bacterial infection before clinicians can know if a positive viral swab alone is enough to abstain from AAP's other recommendations. Similar studies may be warranted to identify rates of dangerous serious bacterial infections such as meningitis in children with other positive results, such as urinalysis and culture. Until further research is completed, a full workup remains the standard for well-appearing febrile infants without an obvious source of infection. Regardless of the above, parental shared decision-making and preferences should always be considered when caring for a child.

Further research will continue to generate new findings that will inform enhancements and updates to the evaluation of well-appearing febrile infants, but the AAP guideline provides clear, evidence-based standards and direction for the workup and treatment of febrile infants ages 8 to 60 days. The guideline offers an opportunity to establish a more cohesive approach to the care planning of this vulnerable age group and encourages variations by clinicians based on individual circumstances and factors present in the infants being evaluated. **JAAPA**

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