Evaluation and Management of Young Febrile Infants: An Overview of the New AAP Guideline

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PRACTICE GAPS/EDUCATION GAPS

There remains variation in the evaluation and management of young febrile infants. This guideline provides the evidence and reasoning necessary for decreasing variation while improving the outcomes for the patient and family.

OBJECTIVES After completing this article, readers should be able to:

1. Evaluate and manage febrile infants aged 8 to 60 days.
2. Engage in shared decision-making with a patient or caregiver when indicated.

ABSTRACT

The American Academy of Pediatrics released a clinical practice guideline for the management of febrile infants in August 2021 to compile nearly 40 years of research into a cohesive text that would provide a framework for the clinician in safely managing these patients in a variety of settings. (1) This guideline incorporates shared decision-making with the caregiver to guide treatment when appropriate and provides algorithms for 3 age groups: 8 to 21 days, 22 to 28 days, and 29 to 60 days. This guideline applies to previously healthy, well-appearing infants born at 37 weeks’ gestation or later who have a temperature of at least 100.4°F (≥38.0°C) in the previous 24 hours at home or in a clinical setting. Infants younger than 8 days and those with diagnosed focal infections are excluded. The highlighted changes to historical practice are in the 2 older age groups. In 22- to 28-day-old infants, if initial laboratory work is normal, shared decision-making is used to direct lumbar puncture and hospital admission with the possibility of monitoring the patient at home or in the hospital. In 29- to 60-day-old infants, admission to the hospital is indicated only if laboratory evaluation is concerning for meningitis or based on clinician judgment. The occurrence of invasive bacterial infection in a febrile infant with a positive viral test is still not well-measured, as broad viral panels are more recently developed technology. As this research evolves and expected advancements in early detection of infectious organisms and biomarkers occur, this new information will need to be incorporated into the existing evidence.

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ABBREVIATIONS

AAP American Academy of Pediatrics
ANC absolute neutrophil count
CPG clinical practice guideline
CRP C-reactive protein
CSF cerebrospinal fluid
GBS group B Streptococcus
HPF high-power field
HSV herpes simplex virus
IBI invasive bacterial infection
IM inflammatory marker
KAS key action statement
PCR polymerase chain reaction
SDM shared decision-making
UA urinalysis
UTI urinary tract infection
WBC white blood cell
INTRODUCTION

In his 1954 article “The Child with a Fever,” Dr Keith Hammond wrote, “Some of them soon develop obvious signs of the disease that is causing the fever. Others, after extensive studies are finally diagnosed, but some just get well and no one is any wiser. A few have been well all the time—their temperature normally runs a little above average.” (2)

This quote is regarding febrile children of all ages but eloquently summarizes the conundrum faced by clinicians when evaluating young infants with fever. This conundrum has led to more than 40 years of research attempting to create an algorithm that would accurately delineate which febrile infants require extensive testing and empirical treatment and which infants can be conservatively managed in the outpatient setting. In fact, the first article in the first issue of Pediatrics in Review in 1979 was about group B streptococcal (GBS) infection in neonates. (3)

Since 2005, experts have been reviewing this collection of research and bringing it together in a cohesive manuscript. (4) In August 2021, the American Academy of Pediatrics (AAP) published a new practice guideline, “Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old.” (1) This guideline provides 7 key action statements (KASs) for each included age group: 8 to 21 days, 22 to 28 days, and 29 to 60 days. This article provides a streamlined overview of the most salient points of the guideline. The guideline itself should be referenced for more in-depth information on each topic and for details about each KAS, including the details of the risks and benefits of each intervention.

BACKGROUND

In the 1980s and 1990s, many groups based in emergency departments conducted studies to determine algorithms for the management and treatment of febrile infants. (5)(6)(7)(8)(9) These initial algorithms included laboratory tests available at the time, such as peripheral white blood cell (WBC) count, band count, and urine WBC count. Although these tests may have utility, inflammatory markers (IMs) such as C-reactive protein (CRP) and procalcitonin levels have been shown to be more useful in the prediction of bacterial infections in febrile infants. Initial standard practice was to monitor infants in the hospital setting for 48 to 72 hours to allow for identification of bacterial pathogens based on manual bacterial culture systems available at the time. Most blood culture systems are now automated and able to identify positive blood cultures more rapidly, and nested polymerase chain reaction (PCR) testing of positive cultures can identify the actual pathogen and common resistance patterns within a few hours. (10)(11) Many facilities have rapid meningitis panels as well, which can potentially enable the clinician to identify pathogens in the cerebrospinal fluid (CSF) within hours. (12)

The epidemiology of bacterial infections has changed since the initial algorithms were developed, which may affect the expected fever response and laboratory criteria described in those original studies. The reason for this shift is multifactorial but likely includes immunization against previously common pathogens such as Haemophilus influenzae and Streptococcus pneumoniae, improvements in food safety and regulation leading to a low incidence of Listeria monocytogenes, and screening for carriage of GBS and prophylaxis if colonization is identified, leading to a decrease in GBS infection in the first week of life. During the past 20 years, Escherichia coli has become the predominant pathogen causing bacteremia as well as urinary tract infection (UTI), and GBS remains the most common cause of bacterial meningitis. (13)(14)(15)(16)

Over the years, it has become apparent that newer testing capabilities could be more useful and that the potential harms of broad testing and treatment may outweigh the risks in many febrile infants. The costs of testing and treatment can be burdensome to families, and for families, the stress of hospitalization is significant. (17)(18) In addition, a study by the Pediatric Research in Office Settings network published in 2004 (19) demonstrated that many community clinicians were safely managing febrile infants outside of the standard algorithms. This study found that participating physicians followed the current guideline for the management of a febrile infant in less than 50% of the patients, but only 2 of 3,066 infants ultimately had a missed invasive bacterial infection (IBI), and those 2 infants had close follow-up with prompt treatment and no adverse outcomes. (19) With recognition of the evolving landscape of testing and epidemiology as well as the evidence that many clinicians were already straying from current published algorithms, the AAP recognized the need for a clinical practice guideline (CPG) for the management of febrile infants.

METHODS

Once the need was identified, the subcommittee of the AAP Council on Quality Improvement and Patient Safety created
a work group of a variety of specialists to create a true representation of the target audience for the guideline. The Agency for Healthcare Research and Quality conducted a systematic review of the literature, and this review was updated over the years of the process to include the newest research. Over a span of approximately 10 years, the working group compiled evidence and discussed the evidence extensively, weighing evolving research and expert opinions. This included 4 meetings at the AAP and many conference calls to create 3 algorithms for the age groups and accompanying KASs. The recommendations are supported with quality of evidence and strength of recommendation per the AAP rating standard. (4)

**TERMINOLOGY**

The term *serious bacterial infection* has classically been used when describing the outcome measure for infections in febrile infants and includes UTI, bacteremia, and meningitis. UTI is much more common than bacteremia or meningitis. For outcomes and terminology, the guideline, therefore, separates UTI from bacteremia and meningitis. The term *IBI* is favored, which includes bacteremia and meningitis.

The “Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old” guideline specifically applies to well-appearing, term, and previously healthy febrile infants. An infant is deemed *well-appearing* by the attending physician, which is acknowledged to be subjective and based on numerous unmeasurable factors, although it must be included as an important variable in prediction. For this guideline, a term *infant* is one born at 37 weeks’ gestation or later. An infant is deemed to be *previously healthy* if he or she does not have suspected immune compromise, major congenital or genetic abnormalities, previous surgery, or treated infections and if there was not a medically significant perinatal course. See Table 1 for more details on the inclusion and exclusion criteria.

**SHARED DECISION-MAKING**

This guideline involves shared decision-making (SDM) between medical providers and caregivers, which is a novel concept in the testing and treatment of febrile infants because previous algorithms have unilaterally directed the physician as to the risks and benefits of testing and treatment. SDM is defined as “a collaborative process in which patients and providers make healthcare decisions together, taking into account the best evidence available as well as the patient’s values and preferences.” (20) Figure 1 is adapted from the Agency for Healthcare Research and Quality SHARE Approach curriculum, which was created to assist clinicians with communication and tools to effectively engage patients in the process of SDM. (21)

When the medical benefit clearly outweighs the risk of testing and treatment, parents should be provided with information about the testing to achieve full transparency of the clinician’s recommendations. When there are 2 or more options for testing and/or treatment, discussing the risks and benefits with the caregiver is preferred and is reflected in the KASs as “Clinicians may ...” statements. In the same arena, the guideline also directly addresses the variance of risk tolerance with both clinicians and caregivers, which affects decision-making. When presented with the same concrete numbers regarding risk of disease or risk of treatment, each person will interpret those numbers differently based on a combination of factors, such as personal experience, personality traits, and colleague or family influence. The most notable opportunities for SDM are in the 22- to 28-day-old group and the 29- to 60-day-old group surrounding the decision for proceeding with lumbar puncture and the decision for hospital admission versus management at home. Although the guideline includes tables of risks and benefits for all procedures and treatments involved, see Table 2 for a summary of...

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**Table 1.** Inclusion and Exclusion Criteria for Applying the Febrile Infant Clinical Practice Guideline

<table>
<thead>
<tr>
<th>INCLUDED</th>
<th>MAY BE INCLUDED</th>
<th>EXCLUDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 8–60 d of age</td>
<td>Upper respiratory tract symptoms</td>
<td>Infants ≤7 d or &gt;60 d of age</td>
</tr>
<tr>
<td>Temperature ≥100.4°F (≥38°C) in past 24 h (at home or in clinical setting)</td>
<td>Diarrhea (unless high concern for bacterial pathogen)</td>
<td>Not well-appearing</td>
</tr>
<tr>
<td>Term infants ≥37 weeks' and &lt;42 weeks' gestation</td>
<td>Recent antibiotic use in infants &gt;2 wk of age</td>
<td>High concern for herpes simplex virus</td>
</tr>
<tr>
<td>Previously healthy</td>
<td>Positive viral testing</td>
<td>Focal bacterial infection</td>
</tr>
<tr>
<td>Well-appearing</td>
<td>Otitis media</td>
<td>Clinical bronchiolitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunizations in previous 48 h</td>
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<tr>
<td></td>
<td></td>
<td>Medically fragile, chromosomal abnormality</td>
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<tr>
<td></td>
<td></td>
<td>Suspected immune compromise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If &lt;2 wk of age and perinatal course with maternal fever or antibiotic use</td>
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</tbody>
</table>
risks and benefits specifically regarding lumbar puncture and hospital admission. In the medical record, the clinician should document the topic of the SDM discussion, highlighting the risks and benefits discussed with the caregiver for each option, the reasoning behind the decision, and the final management plan.

INFLAMMATORY MARKERS

IMs included in the guideline are temperature, absolute neutrophil count (ANC), CRP level, and procalcitonin level. These markers are considered abnormal at the following values: temperature, 101.3°F or greater (≥38.5°C); ANC, greater than 4,000/μL (>4×10⁹/L) or greater than 5,200/μL (>5.2×10⁹/L) (per clinician preference based on the current state of the evidence); CRP level, greater than 2 mg/dL (>20 mg/L); and procalcitonin level, greater than 50 ng/dL (>0.5 μg/L).

The peripheral WBC count and ANC have historically been included in most studies attempting to predict the risk of IBI, but they do not perform well in isolation. The WBC count is not recommended for risk stratification due to its poor performance in screening. The ANC can be a helpful predictive factor in combination with other clinical features or laboratory results. The guideline includes both greater than 4,000/μL (>4×10⁹/L) and greater than 5,200/μL (>5.2×10⁹/L) as cutoff values for abnormal ANCs because 2 separate studies were viewed as reliable for determining these cutoffs and, therefore, were both included. Of note, the study that determined an ANC cutoff value of greater than 4,000/μL (>4×10⁹/L) used the ANC in combination with a urinalysis (UA) and procalcitonin level, whereas the study using greater than 5,200/μL (>5.2×10⁹/L) determined this value methodologically and assigned value as an independent predictor in a scoring tool for the identification of IBI.

The guideline includes a useful overview of the literature that has attempted to quantify the risk of IBI based on the height of fever. Many studies have shown that a higher temperature of 101.3°F or greater (≥38.5°C) increases the likelihood of IBI, although a significant number of infants with IBI will not have a temperature of 101.3°F or greater (≥38.5°C) based on history and initial evaluation. The height of temperature elevation, therefore, should not be used in isolation as a predictive factor for IBI but should be used in combination with other clinical features or laboratory results.

CRP and procalcitonin levels both perform better than the height of fever, WBC count, or ANC as predictive measures for IBI. Procalcitonin level is the best predictor of the currently available tests and rises more quickly than CRP level. Procalcitonin level is recommended by the guideline as the favored IM, although currently this test may not be available or may not be run in a timely manner, depending on the clinical setting. CRP level performs better than ANC and is
likely available at most institutions with a quicker turn-around time for the result and, therefore, may be used when procalcitonin level is not available. If procalcitonin level is available in a timely manner, this should be considered the most reliable IM, even independent of other IMs. If procalcitonin level is not available, the height of fever, ANC, and CRP level should be used together.

**AGE-BASED STRATIFICATION**

Historically, febrile infants younger than 29 days were considered to be at high risk for IBI. Many different studies have worked on identifying a lower age threshold for which an infant is automatically deemed high risk and have shown a decrease in risk with each week of life, although these studies have not come to a definite consensus. The largest studies demonstrated less risk for IBI in the fourth week after birth (19)(28)(29)(30); therefore, this CPG separates this age group into its own algorithm. The guideline does not include infants in the first week of life due to the distinct differences in rates and types of possible infections. In summary, the CPG separates febrile infants into 3 age groups: 8 to 21 days, 22 to 28 days, and 29 to 60 days.

**Infants 8 to 21 Days of Age (Fig 2)**

Infants in this age group should be managed in the hospital. Clinicians should obtain a UA, a urine culture if the UA is positive, a blood culture, a CSF analysis, and a CSF culture and should hospitalize the infant on parenteral antimicrobial treatment while awaiting bacterial culture results. The infant should be discharged after bacterial cultures have remained negative for 24 to 36 hours, the infant is showing clinical improvement, and there is no other reason for hospitalization. The guideline recommends an empirical parenteral antibiotic regimen that includes ampicillin (150 mg/kg per day divided every 8 hours) and either gentamicin (4 mg/kg per dose every 24 hours) or cefazidime (150 mg/kg per day divided every 8 hours). If available, cefotaxime is preferred to cefazidime (150 mg/kg per day divided every 8 hours). If pathogenic bacterial infection is identified in blood, urine, or CSF cultures, the infant should be treated with an antibiotic regimen specifically targeting the identified pathogen.

Of note, the guideline specifies that a urine culture should be performed only if the UA is positive. A positive UA is defined as positive leukocyte esterase, greater than 5 WBCs per high-power field (HPF) in a centrifuged specimen, or greater than 10 WBCs per HPF in an uncentrifuged specimen. This approach to obtaining a urine culture is specified with the intent of decreasing bacterial growth that represents contamination or asymptomatic bacteriuria. In practice, for this age group, the UA should be collected by a sterile method (catheterized or suprapubic aspiration) and the clinician would wait until the UA results have been obtained before ordering the culture with the laboratory. If the caregiver is opposed to sterile urine collection techniques, a nonsterile specimen may be obtained, but culture results should be interpreted with caution given a higher rate of contaminated culture.

IMs may be assessed if the clinician deems them helpful for later decision-making, although the results of IM testing would not alter the initial management in this age group.

**Infants 22 to 28 Days of Age (Fig 3)**

Infants in this age group may be managed at home or in the hospital, depending on the results of initial evaluation and testing. Clinicians should obtain a UA, a urine culture if the UA is positive, blood culture, and IMs. If any IM is positive, CSF analysis and CSF culture should be obtained. If the UA is positive or the CSF analysis suggests bacterial meningitis, then the patient should be hospitalized on parenteral antibiotics while awaiting bacterial culture results.

UA may be obtained by sterile or nonsterile method, although culture should be obtained only by sterile method. A 2-step urine collection process may be functionally difficult in a busy clinical setting, but following this procedure may reduce the urinary catheterization rate significantly. (32)(33)

In this age group, data are limited regarding UTI as a risk factor for meningitis. It is also less likely for an infant to have a febrile UTI without an elevated IM. In the scenario that an infant has a positive UA and negative IMs, the clinician should use clinical judgment and SDM to decide whether to perform a lumbar puncture.

CSF analysis and CSF culture may be performed even if all IMs are normal, the UA is normal, and the infant is already planned to be hospitalized based on clinician judgment and SDM with the caregiver.

If the UA, IMs, and CSF are all normal, the infant may be managed at home with verbal and written instructions given to the caregiver, follow-up within 24 hours, and agreement from the caregiver to return if the infant’s clinical status worsens. If being managed at home, the infant should be given ceftriaxone while awaiting culture results.

If hospitalized, the infant should be discharged once bacterial cultures have remained negative for 24 to 36 hours, the infant is showing clinical improvement, and there is no...
other reason for hospitalization. If pathogenic bacterial infection is identified in blood, urine, or CSF cultures, then the infant should be treated appropriately. The infant may be given parenteral antibiotics if the UA is normal, IMs are normal, and CSF level (if obtained) is normal, based on clinician judgment and with SDM with the caregiver. If administered, intravenous or intramuscular ceftriaxone (50 mg/kg per dose every 24 hours) is recommended.

Infants 29 to 60 Days of Age (Fig 4)
Infants in this age group may be managed at home or in the hospital, depending on results of the initial evaluation and testing. Clinicians should obtain a UA, a urine culture if the UA is positive, a blood culture, and IMs. UA may be obtained by sterile or nonsterile methods, although culture should be obtained only by sterile catheter or suprapubic aspiration. This approach aims to decrease catheterization rates and decrease bacterial growth that represents contamination or asymptomatic bacteriuria.

If UA, IMs, and CSF levels are all normal the infant should be managed at home with verbal and written instructions given to the caregiver, follow-up within 24 hours, and agreement from the caregiver to return if the infant’s clinical status worsens. If being managed at home, the infant need not be treated with antibiotics. If UA and IMs are normal but CSF level is not obtained, the infant may be managed at home without antibiotics based on the clinician’s judgment and SDM with the caregiver.

For infants with an abnormal UA and no abnormal IMs, oral antibiotic therapy may be used while awaiting urine culture results. If the UA is abnormal and an IM is abnormal, the infant may be given parenteral antibiotics.
**Figure 3.** Algorithm for 22- to 28-day-old infants. Key action statement references are in parentheses. CSF = cerebrospinal fluid, HSV = herpes simplex virus, IM = inflammatory marker, LP = lumbar puncture, PCR = polymerase chain reaction, SPA = suprapubic aspiration, T = temperature, UA = urinalysis. (Reprinted with permission from Pantell RH, Roberts KB, Adams WG, et al. Evaluation and management of well-appearing febrile infants 8 to 60 days old. Pediatrics. 2021;148[2]:e202105228.)
after a urine culture is obtained and managed at home or may be admitted to the hospital. Parenteral antibiotics should be discontinued and enteral antibiotics initiated when the urine culture is positive, other bacterial cultures are negative at 24 to 36 hours, and the infant is clinically improving. If a parenteral antibiotic is given with no focus identified or with suspected UTI with an abnormal IM, ceftriaxone is suggested (50 mg/kg per dose every 24 hours). The suggested oral antibiotic choices are either cephalaxin (50–100 mg/kg per day divided every 6 hours) or cefixime (8 mg/kg per dose every 24 hours) to be given empirically until urine culture results direct tailoring of the antibiotic to the most appropriate choice for the continuation of treatment.
CSF level may be obtained if any IM is abnormal but need not be obtained if all IMs are normal. Clinicians should use parenteral antibiotic therapy and hospitalize infants if the CSF level suggests bacterial meningitis. Clinicians may use parenteral antibiotic therapy and hospitalize infants if CSF analysis is normal but any IM is positive. If CSF is positive for enterovirus, clinicians may withhold or discontinue parenteral antibiotic therapy if there are no other factors suggestive of bacterial infection. (33)

**ANTIBIOTIC CHOICE**

When choosing an empirical antibiotic regimen, the clinician should consider the relevant perinatal history and the local antibiogram. Most studies in the past 20 years have demonstrated that *E. coli* is the predominant pathogen causing UTI and bacteremia in infants, and GBS remains a common pathogen in bacteremia and is the most common cause of bacterial meningitis. (13)(14)(15)(16) Empirical antibiotic coverage should, therefore, at least account for these 2 pathogens and may need to account for additional bacteria based on history and laboratory results. Note that cephalosporins are not effective against *Listeria* or *Enterococcus* infections; therefore, ampicillin should be added to the regimen if there is concern for either of these bacteria or if rates in the local community are considered higher than the national average. In addition, if there is a high rate of *E. coli* producing extended-spectrum β-lactamase in a community, then the empirical regimen chosen should include gentamicin (not a cephalosporin), and meropenem should be used in these communities if meningitis is suspected. Ceftriaxone is included in the guideline due to a cefotaxime shortage for many recent years. If available, cefotaxime would be the preferred option. (33)

**HOSPITAL ENVIRONMENT AND DISCHARGE TIMING**

While the infant is hospitalized, the clinician should attempt to optimize the environment for the infant and family by encouraging breastfeeding, providing lactation support, and providing timely communication with the family. The ideal setting is a hospital with nurses and staff experienced in the care of young infants.

When the initial guidance was published, the standard time for monitoring hospitalized infants was 48 to 72 hours. During the subsequent years, this monitoring period decreased to 48 hours because the infant population to be managed focused on term, previously healthy infants. Because it was noted that most blood culture systems were now automated, several studies showed that pathogenic bacteremia in this age group was identified within 36 hours in most patients. (10)(36)(37) Similar studies regarding urine and CSF cultures showed that pathogenic bacterial infection was also typically identified within 36 hours (35)(36)(37); therefore, the “Evaluation and Management of Well-Appearng Febrile Infants 8 to 60 Days Old” guideline recommends that infants be discharged from the hospital at 24 to 36 hours if bacterial cultures remain negative, the infant is clinically improving, and there are no other reasons for ongoing hospitalization.

**COMMENTS ON VIRAL INFECTIONS**

Testing for viral pathogens is evolving, and there are now numerous PCR tests available for a wide array of viruses. Past research has shown that the rates of serious bacterial infection (or IBI) in known cases of influenza, enterovirus, and respiratory syncytial virus are lower than for febrile infants without these viral infections. (38)(39)(40)(41)(42)(43) Newer PCR tests have led to the rapid identification of many other viruses that are likely relevant to the rates of IBI, although there is not currently enough research to firmly identify the risks for these viruses for infants.

Testing for herpes simplex virus (HSV) should be considered if there is CSF pleocytosis, leukopenia or thrombocytopenia, ulcers of mucous membranes or vesicles on the skin, elevated alanine transaminase levels, seizures, hypothermia, maternal genital HSV lesions, or maternal febrile illness in the 48 hours surrounding delivery.

CSF testing for enterovirus can be helpful because the likelihood of bacterial meningitis is low and a positive result for enterovirus could decrease the need for parenteral antibiotics in an infant with CSF pleocytosis. (32)

**FOCUS ON THE FUTURE**

This guideline represents years of discussion and literature review that serves to assist clinicians in all settings with the evaluation and management of febrile infants. There were many controversial topics that were included, such as variance in the management of the “middle age group” of infants 22 to 28 days of age and the exclusion of infants younger than 8 days of age. Although incredibly helpful, the guideline was not able to encompass all areas surrounding the management of febrile infants. In future revisions, it may be helpful to the clinician for the guideline to expound on areas surrouding viral infections, specifically, more detailed guidance on the evaluation for HSV infection and data regarding the risk of IBI in the setting of a positive viral test.
CONCLUSIONS

The “Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old” guideline provides information from a generous collection of the research regarding febrile infants during the past 40 years and compiles this evidence into practical algorithms for well-appearing febrile infants in the infant age groups of 8 to 21 days, 22 to 28 days, and 29 to 60 days. This guideline also provides details regarding SDM on testing and treatment, choice of testing and treatment, disposition, and follow-up guidance. There are factors still in evolution, such as the effect of broad viral testing capabilities and the risk of concurrent IBI that may influence future iterations of the guideline. This guideline should be interpreted in the context of the clinician’s and caregiver’s risk tolerance, in combination with factors such as the health-care setting, financial and social concerns, availability for patient follow-up, and access to care. In addition, it should be noted that the epidemiology of bacterial infections will change over time and may vary between regions, which should be considered by the clinician.

Summary

- Based on strong evidence and consensus, testing capabilities have improved and the epidemiology of bacterial infections has changed since the initial algorithms for managing febrile infants were created; therefore, new guidance was needed. (10)(11)(13)(14)(15)(16)

- Based on some research and consensus, when there is more than 1 safe option for testing or treatment, the clinician should engage in shared decision-making with the caregiver regarding the best treatment option. (20)

- Based on moderate research evidence, the risk of invasive bacterial infection decreases with each week after birth and is notably less after the fourth week after birth. The “Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old” guideline, therefore, is separated into 3 age groups with a tiered approach for evaluation and management based on age. (19)(28)(29)(30)

  - Based on strong research evidence, inflammatory markers (IMs) should be obtained and may direct further evaluation in both the 22- to 28-day-old infant group and the 29- to 60-day-old infant group. Procalcitonin level is the IM with the best predictive value to detect invasive bacterial infection, and C-reactive protein level remains helpful as well. Height of temperature and absolute neutrophil count are less helpful but may be used if preferred testing is not available. (21)(22)(23)

  - Based on strong research evidence, if a febrile infant is admitted to the hospital, the infant should be discharged once bacterial cultures have remained negative for 24 to 36 hours. (35)(36)(37)

  - Based on strong research evidence, oral antibiotics may be used in the 29- to 60-day-old infant group with outpatient management while awaiting the urine culture results if the infant has an abnormal urinalysis result and no abnormal IMs, follow-up is available within 24 hours, and verbal and written instructions are provided to the caregiver. (44)

ACKNOWLEDGMENTS

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References for this article can be found at https://doi.org/10.1542/pir.2022-005624.
1. A 25-day-old girl presents to the emergency (ED) because her father noted that her temperature was 101.3°F (38.5°C). She was still breastfeeding without any apparent decrease in urination. Labor and delivery were uncomplicated, and the mother had no fever before or after delivery. The mother has no history of genital herpes simplex virus. In the ED the girl’s temperature is 100.5°F (38.1°C) and her other vital signs are normal. She seems to be alert and visually tracks. She has no skin lesions or rash, and the remainder of her examination findings are normal. Which of the following would be the best independent predictor of an invasive bacterial infection for this patient?
   A. Absolute neutrophil count.
   B. Height of fever.
   C. Immature/total neutrophil ratio.
   D. Procalcitonin level.
   E. White blood cell count.

2. A 14-day-old girl is seen in the office for a temperature of 101.5°F (38.6°C). Pregnancy, labor, and delivery were uncomplicated. The mother states that she has continued to breastfeed. On examination her temperature is 101.5°F (38.6°C), her heart rate is 155 bpm, her respiratory rate is 40 breaths/min, and her oxygen saturation on room air is 98%. She is not toxic-appearing, and there are no focal findings on examination. A urinalysis, complete blood cell count, and blood culture are obtained, and results are pending. Which of the following is the most appropriate next step in management?
   A. Admit to the hospital, obtain a C-reactive protein (CRP) level, and do not perform lumbar puncture if her CRP level is less than 3.5 mg/dL (<35 mg/L) and her urinalysis findings are normal.
   B. Admit to the hospital, obtain a procalcitonin level, and do not perform lumbar puncture if her procalcitonin level is less than 125 ng/dL (<1.25 mg/L).
   C. Admit to the hospital, obtain urine culture if her urinalysis is positive, and perform a lumbar puncture.
   D. Administer intramuscular ceftriaxone and discharge on amoxicillin/clavulanate if the urinalysis results and complete blood cell count (CBC) are normal.
   E. Obtain CRP and discharge to home if the urinalysis and CBC are normal and her CRP is less than 40 mg/L.

3. An 8-day-old boy is seen in the ED with a history of a temperature at home of 100.8°F (38.2°C). The infant is breastfeeding appropriately. His temperature in the ED is 101.3°F (38.5°C), and his physical examination findings are normal. His mother denies any history of genital herpes, and she had no peripartum or postpartum fever. A CRP level is 2.7 mg/dL (27 mg/L), and his alanine transaminase level is normal for age. Urinalysis, blood culture, and cerebrospinal fluid (CSF) studies are pending. Which of the following is the most appropriate empirical antimicrobial regimen?
   A. Intravenous (IV) ampicillin and cefazidime.
   B. IV ampicillin and vancomycin.
   C. IV cefazidime and vancomycin.
   D. IV ceftriaxone, vancomycin, and acyclovir.
   E. Oral acyclovir, IV cefazidime, and IV gentamicin.
4. A 23-day-old girl presents to the ED with her parents for a history of suspected fever at home. Her parents state that she felt warm and seemed somewhat more fussy than usual. They state that they do not have a functional thermometer. Her temperature in the ED is 101.3°F (38.5°C). She is crying but is consoled being held by her mother. Her physical examination findings are normal. Blood culture is obtained. Procalcitonin has a 2-day turnaround time for the result, so it is not ordered. A CRP level is 4.2 mg/dL (42 mg/L), and her absolute neutrophil count is 5,500/µL (5.5 × 10⁹/L). A catheterized urine specimen is obtained, and the urinalysis has 2+ leukocyte esterase. Urine culture is ordered. Which of the following is the most appropriate next step in management?

A. Admit to the hospital and begin empirical acyclovir and ceftazidime.
B. Admit to the hospital and begin empirical ceftazidime.
C. Discharge on oral cephalexin with follow-up the next day.
D. Lumbar puncture, admit to the hospital, and begin parenteral antibiotics.
E. Lumbar puncture and discharge on oral cephalexin if the CSF cell count is normal and the multiplex polymerase chain reaction panel is negative.

5. A 7-week-old girl presents to the ED with her parents because she felt warm and her mother recorded a temperature of 101.0°F (38.3°C). She has continued to breastfeed appropriately and has had a normal number of wet diapers. She is alert, interactive, and smiles at her mother. Her temperature in the ED is 100.5°F (38.1°C), and the remainder of her examination findings are normal. A blood culture, CBC, and procalcitonin level are ordered. The white blood cell count is 10,200/µL (10.2 × 10⁹/L) and the absolute neutrophil count is 2,200/µL (2.2 × 10⁹/L). Her procalcitonin level is 20 ng/dL (0.2 µg/L). A catheterized urine specimen is obtained, and the leukocyte esterase is 2+ positive and the nitrite is positive. Urine culture is ordered. Which of the following is the most appropriate next step in management?

A. Admit to the hospital, perform lumbar puncture, and begin IV ceftazidime and vancomycin.
B. Admit to the hospital, perform lumbar puncture, and begin IV ceftriaxone.
C. Admit to the hospital, perform lumbar puncture, and begin IV gentamicin.
D. Discharge with oral cephalexin if parents agree to observe and communicate any change in the baby’s condition, have reliable transportation, and ensure follow-up within 24 hours.
E. Perform lumbar puncture and discharge with oral amoxicillin if the CSF cell count is normal and her parents agree to observe and communicate any change in the baby’s condition, have reliable transportation, and ensure follow-up within 24 hours.