American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Clinical Practice Guideline: Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old

Robert H. Pantell, MD, FAAP,[a] Kenneth B. Roberts, MD, FAAP,[b] William G. Adams, MD, FAAP,[c] Benard P. Dreyer, MD, FAAP,[d] Nathan Kuppermann, MD, MPH, FAAP, FACEP,[e] Sean T. O'Leary, MD, MPH, FAAP,[f] Kymika Okechukwu, MPA,[g] Charles R. Woods Jr, MD, MS, FAAP[h] SUBCOMMITTEE ON FEBRILE INFANTS

abstract

This guideline addresses the evaluation and management of well-appearing, term infants, 8 to 60 days of age, with fever ≥38.0°C. Exclusions are noted. After a commissioned evidence-based review by the Agency for Healthcare Research and Quality, an additional extensive and ongoing review of the literature, and supplemental data from published, peer-reviewed studies provided by active investigators, 21 key action statements were derived. For each key action statement, the quality of evidence and benefit-harm relationship were assessed and graded to determine the strength of recommendations. When appropriate, parents' values and preferences should be incorporated as part of shared decision-making. For diagnostic testing, the committee has attempted to develop numbers needed to test, and for antimicrobial administration, the committee provided numbers needed to treat. Three algorithms summarize the recommendations for infants 8 to 21 days of age, 22 to 28 days of age, and 29 to 60 days of age. The recommendations in this guideline do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

[a]Department of Pediatrics, School of Medicine, University of California San Francisco, San Francisco, California; [b]Department of Pediatrics, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [c]Boston Medical Center/Boston University School of Medicine, Deparment of Pediatrics, Boston, Massachusetts; [d]Department of Pediatrics, NYU Grossman School of Medicine, New York, New York; [e]Departments of Emergency Medicine and Pediatrics, School of Medicine, University of California, Davis School of Medicine, Sacramento, California; [f]Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, Colorado; [g]American Academy of Pediatrics, Itasca, Illinois; and [h]Department of Pediatrics, Children's Hospital at Erlanger and College of Medicine, The University of Tennessee at Chattanooga, Chattanooga, Tennessee

The recommendations in this guideline do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

All clinical practice guidelines from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

DOI: https://doi.org/10.1542/peds.2021-052228

Address correspondence to Robert H. Pantell, MD. E-mail: Robert.Pantell@UCSF.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

To cite: Pantell RH, Roberts KB, Adams WG, et al. Clinical Practice Guideline: Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old. *Pediatrics*. 2021;148(2):e2021052228

BACKGROUND

Efforts to develop an evidence-based approach to the evaluation and management of young febrile infants have spanned more than 4 decades.[1] In the 1970s, concerns arose about the emergence and rapid progression of group B *Streptococcus* (GBS) infection in neonates, whose clinical appearance and preliminary laboratory evaluations did not always reflect the presence of serious disease.[2] Such concerns led to extensive evaluations, hospitalizations, and antimicrobial treatment of all febrile infants younger than 60 days,[3] with many institutions extending complete sepsis workups to 90 days. However, the seminal

1983 study by De Angelis et al[4] highlighted the iatrogenic complications that accompany hospitalizing young, febrile infants and provided an impetus for developing clinical strategies that would be more selective for hospitalizations. Today, the consequences of medical errors during hospitalizations are well known.[5–7]

In the 1980s and 1990s, there were numerous efforts to develop and validate clinical prediction models for detecting serious bacterial illness (SBI).[8–15] Efforts were hampered by the heterogeneity of the definition of SBI. Some studies included clinically obvious infections such as cellulitis. Others included pneumonia, which may be viral or bacterial; many included bacterial gastroenteritis in infants with diarrhea. All included urinary tract infection (UTI), bacteremia, and bacterial meningitis, but UTI is so much more common than the other infections that it distorts models attempting to identify all causes.

These prediction models involved a combination of clinical and laboratory test parameters that were based on a priori criteria and were not derived from the primary data. Each variable was defined arbitrarily, such as age groupings in weeks or months and integers ending in zero, for which there is no real physiologic or biological basis. For example, the variable that defined an abnormal white blood cell (WBC) count as <5000 per mm^3 or $>15\,000$ per mm^3 was not statistically derived but established in advance as an indicator and tested in combination with other predictor variables.

Recommendations emerged that generally relied on clinical appearance, age, urinalysis, WBC count (and/or absolute neutrophil count [ANC], band count, and/or immature to total neutrophil ratio), and cerebrospinal fluid (CSF) analysis (except for the Rochester criteria, which did not require CSF).[10] All had somewhat similar sensitivities and specificities as well as predictive values. The models were promulgated because of moderately high sensitivities (90% to 95%) and high negative predictive values (NPVs) (97%–99%). The high NPVs were expected because of the uncommon occurrence of the most serious infections, which, along with modest specificities (20% to 40%), also explained the relatively low positive predictive values.

A major shift occurred in the mid-1980s when Powell et al in Rochester accepted the inability to predict who was at high risk and attempted instead to predict who was at low risk, even in the first month of life.[10,14] A pattern emerged in which it was recommended that all infants in the youngest group (<29 days of age) should receive extensive evaluations, hospitalization, and empirical antimicrobial treatment, and infants 29 to 90 days of age could be managed with presumptive intramuscular ceftriaxone as outpatients with pending blood, urine, and CSF culture results.[15]

In time, other groups used techniques to develop clinical prediction rules that rely on gathered data to derive and define the best, most precise, and parsimonious set of variables that predict a defined outcome that can be translated into recommendations.[16–18] Still another approach was the sequential approach of established clinical and laboratory criteria.[19,20] Despite these substantial efforts, there has been ongoing evidence that community and emergency physicians do not routinely follow these recommendations in real-world settings.[17,21–27] Clinical outcomes have not been shown to suffer despite nonadherence to contemporaneous standards of care.

Differing approaches to the management of very young febrile infants indicated the need for a guideline that is current, evidence-based, and developed by a national professional society or organization with broad representation. This led the American Academy of Pediatrics (AAP) to embark on developing this guideline with the assistance of an evidence review commissioned by the Agency for Healthcare Research and Quality (AHRQ).[26]

Attention has been given to the following present-day considerations:

1. Changing Bacteriology

Since the 1980s, the epidemiology of bacterial infections in neonates and infants has changed as a result of many factors, including prenatal GBS screening and incorporation of immunization against *Streptococcus pneumoniae.* Furthermore, improvements in food safety may have resulted in a decrease in the incidence of disease caused by *Listeria monocytogenes* in this age group. Recent studies demonstrate that *Esherichia coli* is now the most common organism to cause bacteremia, while GBS remains the most common cause of meningitis in most studies.[25,27–31] Infections with *L monocytogenes* are now rare in the United States.[32,33] The shift from Gram-positive to Gram-negative predominance has implications for the choice of tests, interpretation of values for decision-making, and the selection of antimicrobial drugs. Using the decision models of the 1980s today can lead to misclassification of bacterial meningitis in 23.3% to 32.1% of cases.[34]

2. Cost of Unnecessary Care

Studies indicate significant variation in care and consequently considerable differences in costs.[17,22–24] Differential access, delays, language barriers, and fragmented care can also be costly to infants, families, and the health care system. A substantial basis for practice variability among clinicians is attributable to differences in infants' clinical presentations and severities of illness. However, more than 50% of the variability has been unexplained.[35] Beyond unnecessary hospitalizations, and financial and social costs, there are also potential harms from hospital-acquired infections and iatrogenesis in prolonged hospitalizations.

Costs are justified on the basis of the magnitude of the benefit and/or reduction of potential harms. In studies of prediction models, instances of missed invasive bacterial infections (IBI) in well-appearing low-risk infants are uncommon. For infants not managed according to existing clinical prediction models, there are also uncommon misses reported in the literature. These factors suggested there is an opportunity to "safely do less."[36]

3. Advances in Testing

Inflammatory Markers

The WBC, ANC, and band count, combined with clinical appearance and urinalysis, have been the foundation of earlier clinical prediction models. With *E coli* replacing GBS as the most common bacterial pathogen in this age group, these markers are no longer as useful. C-reactive protein (CRP), an inflammatory marker (IM) produced by the liver in response to infections and numerous other conditions, is now available for point-of-care testing.[37] Procalcitonin, expressed mainly by thyroid C cells, is produced rapidly in response to infection and other tissue injuries. It is more specific for bacterial infections than other IMs and rises more quickly to abnormal values. Procalcitonin has emerged as the most accurate IM for risk stratification available, although not currently available at many sites in the United States with timely results on a 24/7 basis.[38,39] (See additional discussion in KAS 10)

Pathogen Identification

There have been improvements allowing more accurate screening for invasive infections and more rapid and precise identification of bacterial, viral, and fungal pathogens. Automated blood culture systems can now identify most bacterial pathogens in <24 hours. Most recently, nested multiplex polymerase chain reaction (PCR) testing of positive blood cultures can identify bacterial pathogens and antimicrobial resistance genes in approximately 1 hour.[40–42] Similarly, multiplex meningoencephalitis panels can provide results on CSF for 14 potential CSF pathogens in 1 hour.[43]

Viral Testing

The development of rapid viral PCR and multiplex respiratory viral testing has led to identifying emerging agents, such as parechovirus, and prompted analyses of their effect on risk stratification of young febrile infants.[44–53] Although the presence of documented respiratory viral infections decreases the risk of IBIs in febrile infants (see Inclusion Criteria 5, Positive viral test), it remains unclear how a positive viral test result should influence further laboratory evaluation and management, especially in the first month of life. In addition, it is unclear whether a positive viral test result will either obviate or shorten hospitalization. Researchers in a study analyzing data before the widespread availability of multiplex viral testing (2000–2012) did not find a difference in length of stay between febrile infants with or without positive viral test results.[54] More work is needed, and this is included as an important question in Future Research.

Emerging Technologies

The area of genomic diagnostics for IBIs is still in its relative infancy, including both genomic identification of viral and bacterial genetic material as well as identifying host genomic responses to viral or bacterial infections. Both need further work to see how these technologies compare in accuracy and timing to routine diagnostic techniques. But progress is being made for RNA transcriptional profiling[55] and next-generation sequencing of microbial cell-free DNA.[56]

4. Opportunities to Improve the Care of Hospitalized Infants

Advances in testing and clinical strategies can speed discharge. Data indicate that including evidence-based strategies in care process models can improve infant outcomes.[57] Hospital environments can be stressful for parents but can be restructured to support maternal/child bonding and breastfeeding.[58] See further discussion in KAS 6.

5. Evolving Research Strategies

Although early studies largely emanated from single-site inner-city emergency departments (EDs), recent investigations conducted by large, geographically widespread research networks and integrated regional health care systems have developed more generalizable evidence.[17–20,22,25,57] Advances in data storage and analysis as well as adoption of statistical procedures[59] for developing clinical prediction rules offer advantages compared with earlier efforts. Collaborative efforts of primary care practices, EDs, hospitals, and integrated health systems are creating larger and more refined data sets. With personalized medicine, enabled by these large data sets and evolving modeling techniques capable of analyzing infants on dozens of variables, the committee anticipates that in the future we will see "one child, one guideline."

This guideline, grounded in continually expanding evidence and including new technologies, should, for today's clinicians, form the foundation on which a more nuanced and precise approach can be used to develop an optimal strategy for evaluating and managing each febrile infant. The committee encourages use of the 3 age-based algorithms in Figs 1–3 as a guide to arriving at the best approach. Approaches may differ somewhat depending on many perinatal or neonatal factors, clinician's experience, parents' abilities and values, nature of relationship with the infant's family, characteristics of the clinical setting, and ability to obtain timely laboratory results, among others.

EVIDENCE FOR AGE-BASED RISK STRATIFICATION

Ongoing research has challenged classifying all infants younger than

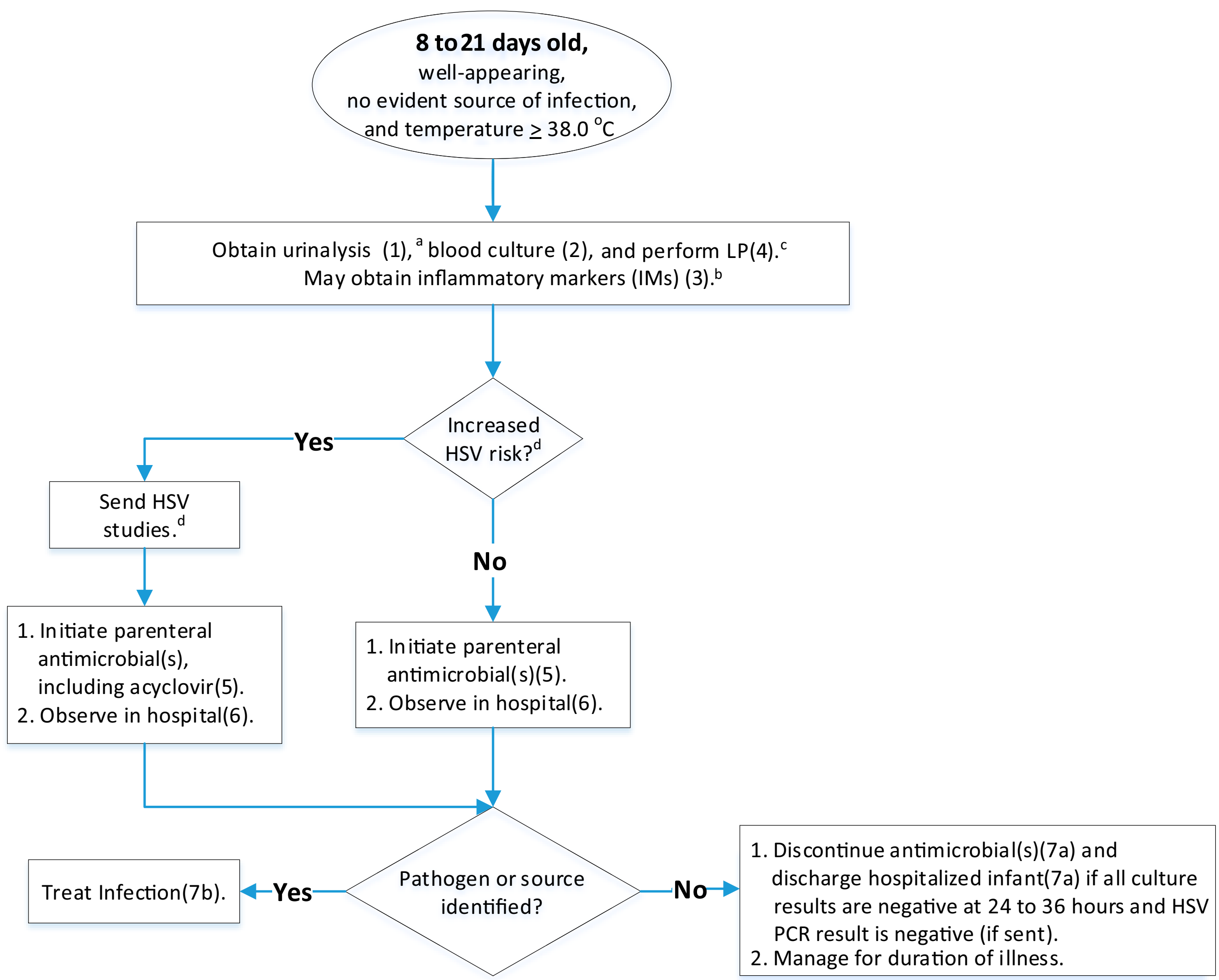

FIGURE 1 Algorithm for 8- to 21-day-old infants. [a] KAS references are shown in parentheses. [b] Laboratory values of inflammation are considered elevated at the following levels: (1) procalcitonin >0.5 ng/mL, (2) CRP >20 mg/L, and (3) ANC >4000, >5200 per mm^3 (see text). Although we recommend all infants in this age group have a complete sepsis workup, receive parenteral antimicrobial agents, and be monitored in a hospital, knowing IM results can potentially guide ongoing clinical decisions. [c] Send CSF for cell count, Gram stain, glucose, protein, bacterial culture, and enterovirus PCR (if available) if pleocytosis is present and during periods of increased local enterovirus prevalence. [d] HSV should be considered if the mother has genital HSV lesions or fever from 48 hours before to 48 hours after delivery and in infants with vesicles, seizures, hypothermia, mucous membrane ulcers, CSF pleocytosis in the absence of a positive Gram stain result, leukopenia, thrombocytopenia, or elevated alanine aminotransferase levels. For further discussion, see the current *Red Book*. Recommended HSV studies are CSF PCR; HSV surface swabs of the mouth, nasopharynx, conjunctivae, and anus for an HSV culture (if available) or PCR assay; alanine aminotransferase; and blood PCR.

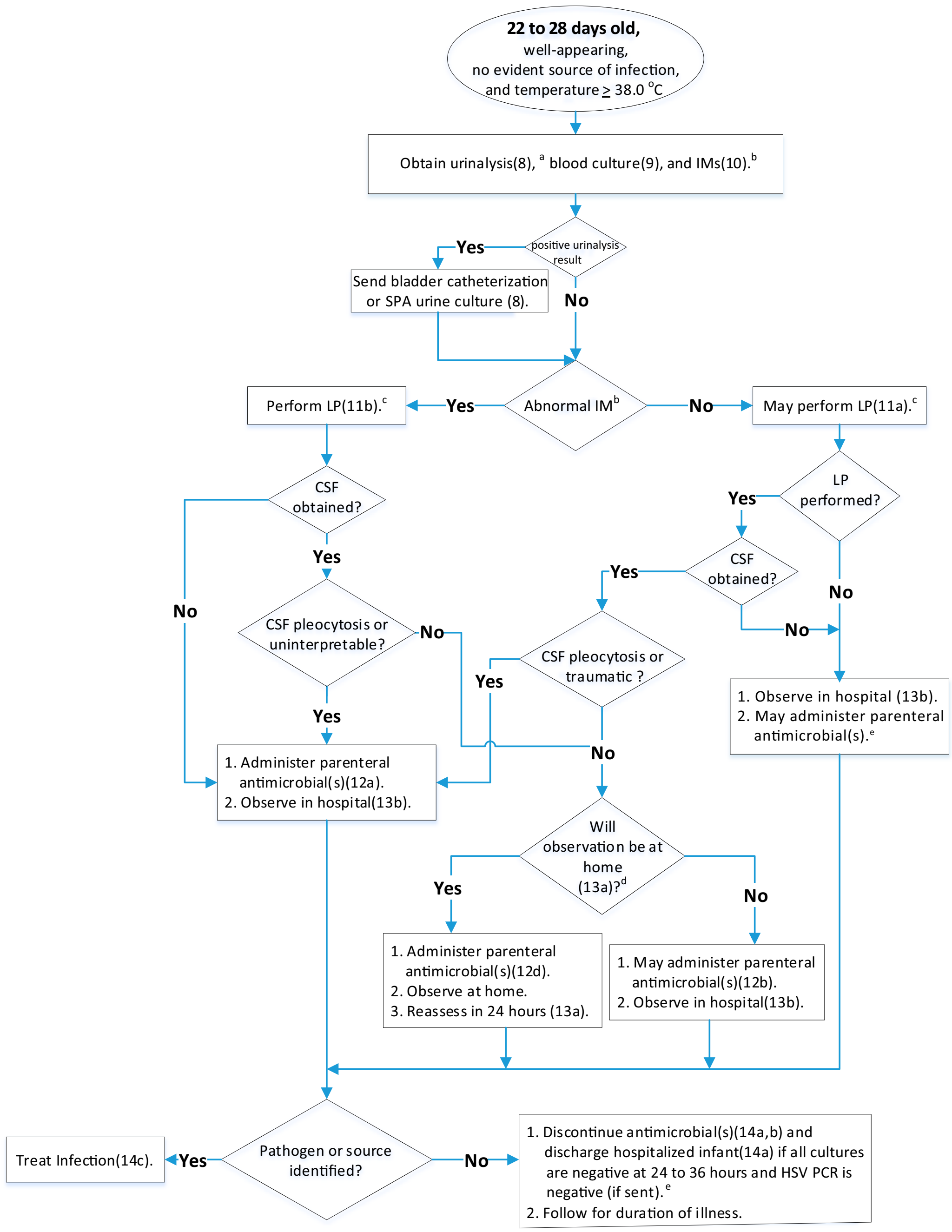

FIGURE 2 Algorithm for 22- to 28-day-old infants. [a] KAS references are shown in parentheses. [b] If available, procalcitonin (PCT) should be obtained along with ANC. If PCT is unavailable, ANC and CRP should be obtained, and a temperature >38.5°C is considered abnormal. PCT is considered abnormal at >0.5 mg/mL; CRP is considered abnormal at >20 mg/L; ANC is considered abnormal at >4000 when used in conjunction with PCT or >5200 when PCT is unavailable (see text). [c] LP is recommended before administration of antimicrobial agents because interpreting CSF after the administration of antimicrobial agents is difficult. However, the risk of meningitis in 22- to 28-day-old infants is lower than that in infants <22 days old in several studies. Therefore, in some circumstances, clinicians may elect to defer an LP and initiate antimicrobial agents, recognizing the potential risk of partially treated meningitis. Send CSF for cell count, Gram stain, glucose, protein, bacterial culture, and enterovirus PCR (if available) if pleocytosis is present and during periods of increased enterovirus prevalence. HSV can occur in this age group. HSV should be considered in infants with vesicles, seizures, hypothermia, mucous membrane ulcers, CSF pleocytosis in the absence of a positive Gram stain result, leukopenia, thrombocytopenia, or elevated alanine aminotransferase levels. For further discussion, see the current *Red Book*. Recommended HSV studies: CSF PCR; HSV surface swabs of mouth, nasopharynx, conjunctivae, and anus for HSV culture (if available) or PCR assay; alanine aminotransferase; and blood PCR. [d] Infant may be managed at home if parent and clinician agree that the following are present: reliable phone and transportation, parent willingness to observe and communicate changes in condition, and agreement to the infant being reevaluated in 24 hours. [e] If CSF is positive for enterovirus, clinicians may withhold or discontinue antimicrobial agents and discharge at 24 hours, provided they meet other criteria for observation at home.

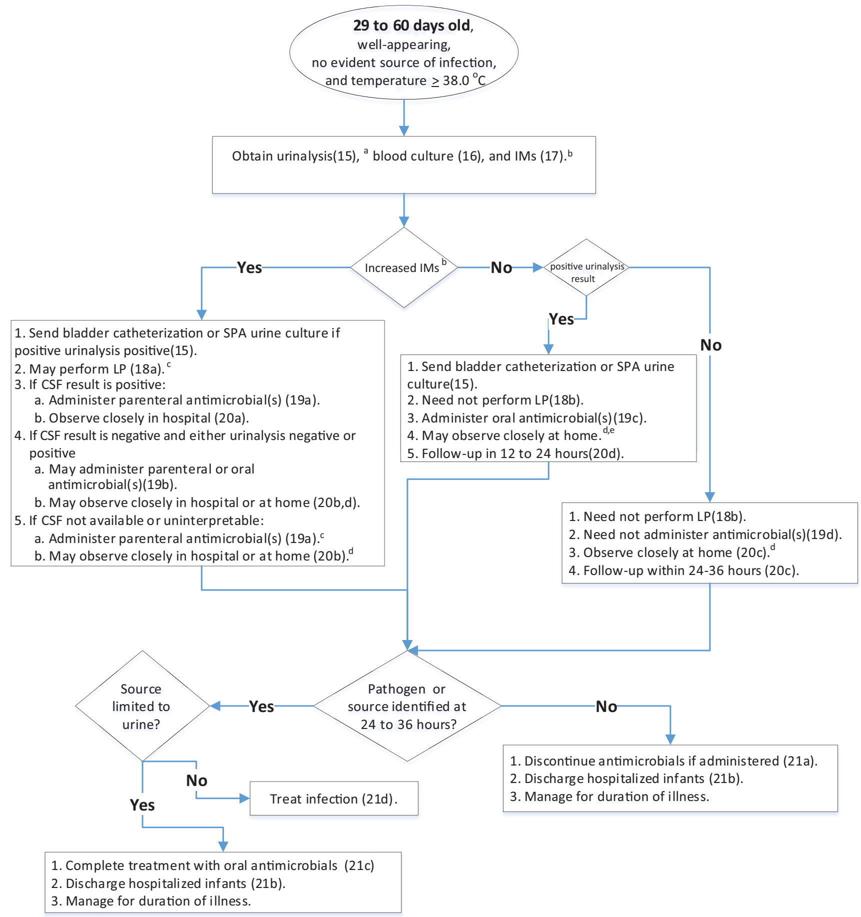

FIGURE 3 Algorithm for 29- to 60-day-old infants. [a] KAS references are shown in parentheses. [b] If available, procalcitonin (PCT) should be obtained along with ANC. If PCT is unavailable, ANC and CRP should be obtained, and a temperature >38.5°C is considered abnormal. PCT is considered abnormal at >0.5 mg/mL; CRP is considered abnormal at >20 mg/L; ANC is considered abnormal at >4000 when used in conjunction with PCT or >5200 when PCT is unavailable (see text). [c] Send CSF for cell count, Gram stain, glucose, protein, bacterial culture, and enterovirus PCR (if available) if CSF pleocytosis is present and during periods of increased local enterovirus prevalence. Although uncommon in this age group, HSV should be considered when there is a maternal history of genital HSV lesions and in infants with vesicles, seizures, hypothermia, mucous membrane ulcers, CSF pleocytosis in the absence of a positive Gram stain result, leukopenia, thrombocytopenia, or elevated alanine aminotransferase levels. For further discussion, see the current *Red Book*. Recommended HSV studies are CSF PCR; HSV surface swabs of mouth, nasopharynx, conjunctivae, and anus for HSV culture (if available) or PCR assay; alanine aminotransferase; and blood PCR. If CSF is unobtainable or uninterpretable, there are insufficient data to make a specific recommendation. Options include the following: observe without treatment for a period of time and, depending on infant clinical condition, repeat LP and/or laboratory markers; begin empirical antimicrobial agents and reassess in 24 hours on the basis of infant response and results of blood culture; if CSF is bloody or antimicrobial agents have previously been started, analysis by multiplex PCR can add additional information; consult with local a pediatric infectious disease specialist. [d] Infant may be managed at home if parent and clinician agree that the following are present: reliable phone and transportation, parent willingness to observe and communicate changes in condition, and agreement to the infant being reevaluated in 24 hours. [e] Most 29- to 60-day-old infants with negative IM and urinalysis results may be observed at home. However, hospital observation is an option for infants when there are barriers to follow-up.

29 days as high risk. The Pediatric Research in Office Settings (PROS) study indicated that when combined with other variables, infants >25 days of age were at low risk for IBIs, 0.4%.[17] Subsequently, the European Collaborative Group developed and validated the step-by-step approach with a combination of clinical and laboratory variables that included 22- to 28-day-old infants, capable of identifying infants at low risk for IBIs, ranging from 0.2% to 0.7%.[19,20] A recent scoring system methodologically derived by Aronson et al identified age >21 days to be useful in identifying low-risk infants.[60] In a prospective study of 4778 infants from the Pediatric Emergency Care Applied Research Network (PECARN), there was a significantly lower rate of bacteremia in the fourth week (1.6%) compared with weeks 2 (5.3%) and 3 (3.3%) and no difference from weeks 5 and 6

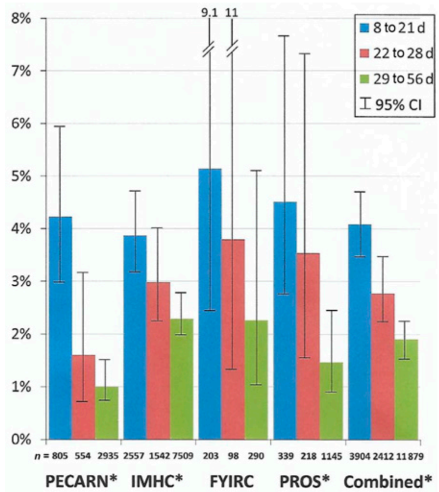

FIGURE 4 Rate of bacteremia by age groupings. * χ^2 for trend: $P < .001$. Note that the 95% CIs in the combined group do not overlap. Data were adapted from reference 61; from reference 94, with detail provided by C.L.B. (personal communication, 2020); from reference 24, with detail provided by Paul Aronson (personal communication, 2020); and from reference 17, with detail provided by Matthew Pantell (personal communication, 2020). FYIRC, Febrile Young Infants Research Collaborative; IMHC, University of Utah/Intermountain Healthcare.

($P = .76$).[61] A prospective national surveillance study in England analyzed 22 075 episodes of IBI from 2010–2017.[62] This population-based analysis documented a dramatic decrease in IBI after the first week of life, followed by a continuous stepwise decrease in population incidence over the next 8 weeks. The decline in bacteremia prevalence by age for regional and national studies is portrayed in Fig 4.

Because risk of IBI has extensively been documented to steadily decline over the first few months, any day or week cutoff is arbitrary and subject to interpretation depending on a clinician's or a parent's risk aversion or tolerance. These data form the basis for the committee developing a separate algorithm for infants 22 to 28 days of age.

CHALLENGES

A number of unique challenges confronted the development of an evidence-based approach to the febrile infant.

1. The initial challenge was to decide whether to include infants in the first week of life. The committee decided early on that infants in the first week of life are sufficiently different in rates and types of illness, including early-onset bacterial infection, that they should be excluded from this guideline.
2. Many published studies used SBI as an outcome measure. Because SBI is not a single clinical entity, analyses fell short of identifying the risks for specific infections. UTI is so much more common than the other bacterial infections that it can distort the accuracy of a prediction model to detect bacteremia or bacterial meningitis. This guideline addresses evidence for bacterial meningitis and bacteremia separately from UTIs; the committee strongly discourages further use of the term "SBI."
3. Meningitis, the most serious bacterial infection responsible for infants' fevers, is uncommon. Accumulating a large enough sample size to be able to accurately predict infrequent infections is a major research challenge; an even larger sample size is required to address the morbidity and long-term consequences accompanying meningitis.
4. As the epidemiology of bacterial species responsible for infections is continually changing, a prediction model or rule developed today will not necessarily be valid in the future. Species types and resistance patterns also vary geographically.
5. Existing clinical prediction models as well as prediction rules often rely on "clinical appearance," well versus ill, a subjective assessment.[8–17,19,20] Despite an elegant process of development, the Yale Observational Score,[8] a formal scoring system for illness appearance, has not proven to be useful in this age group.[63,64] The accuracy of clinician assessment is likely related to experience. Unfortunately, there is no measure or adequate definition for what constitutes "experienced," or of "well appearing." Researchers in large studies have often treated clinical appearance as binary: well appearing or not, or ill appearing or not. When offered 3 categories, however, both senior residents[65] and experienced pediatricians[17] classified a quarter of the young febrile infants they encountered in an intermediate category, acknowledgment that the distinction between "well" and "ill" is not always clear-cut. The distinction is likely to be most difficult before the emergence of the social smile, which enables the infant to "respond to social overtures," a key element in the Yale Observational Score.[8] Clinicians differ in a variety of ways including knowledge, clinical experience with febrile infants, and in the time available to evaluate and monitor infants. The committee acknowledges that some clinicians may have different levels of experience and

confidence in determining well appearance compared with experienced pediatricians.
6. Clinicians work in different settings with a range of familiarity with their patients and families, access to medical records, and abilities to follow-up with patients in a timely fashion.
7. Clinicians have variable access to newer diagnostic tests and timely results, particularly procalcitonin.
8. Families possess a spectrum of knowledge and skills to continuously observe and assess infants discharged from the hospital. Multiple factors may affect a timely return visit. There has been considerable interest focused on shared decision-making for young febrile infants,[66–70] including a recent mobile device app to help clinicians communicate with parents.[71]

For purposes of this guideline, the committee believes that at a minimum, families should be provided with information about the risks and benefits of all procedures, including invasive procedures such as a lumbar puncture (LP) and a bladder catheterization. An opportunity for questions and dialogue between the family and care team should be provided. Families' decisions about their infant will be made in the context of their previous experiences with the health system, their personal beliefs and values, and knowledge and understanding of their child's condition and diagnostic and treatment options and outcomes.

The decision to actively monitor an infant at home or in the hospital requires a collaborative discussion between the family and the care team. The discussion should be centered on the best interest of the child, taking into account the family's and the care team's assessment of the multiple factors of risk and risk tolerance, experience and comfort of monitoring an ill infant, and ease and accessibility of transportation. Academic medical centers and children's hospitals generally provide high-quality observation for ill infants, as do many community hospitals with dedicated pediatrics units. Many hospitals do not have nurses and staff with experience and skills caring for young infants, however. In the current health care system, insurance status and coverage may further affect the family's and care team's decision on location of monitoring.

RISK TOLERANCE: A NUMBER IS NOT A DECISION

Even with the availability of valid and reliable data, thoughtful investigators and clinicians will have different thresholds for recommending diagnostic tests and therapeutic interventions. The committee believes understanding risk tolerance is of fundamental importance to guideline interpretation. In a straightforward case of a febrile infant having CSF pleocytosis with a predominance of polymorphonuclear leukocytes and a positive Gram stain result, the committee would expect clinicians to unanimously agree the infant be hospitalized and receive immediate antimicrobial treatment. Similarly, on the basis of prevalences cited in KAS 1, 8, and 15, a risk for UTI can be estimated at 10%, which translates to a recommendation to perform 10 urinalyses to detect a single UTI, or a number needed to test of 10. This is an example in which agreement to perform a urinalysis is expected. However, challenges frequently occur. For example, if clinical and laboratory evaluations suggest the likelihood of bacteremia is 1:100 (number needed to treat = 100) or a risk of bacterial meningitis at 1:1000 (number needed to test = 1000), is it worth 100 doses of antibiotics to treat a single case of bacteremia while awaiting blood culture results? Should the committee recommend performing the number of LPs required to obtain 1000 samples of interpretable CSF to prevent a delay in recognizing and treating a single case of bacterial meningitis? Responses to these questions depend on how much risk is considered tolerable. The challenge in guideline development was succinctly stated as, "Thus, evidence alone never speaks for itself or conveys the truth because it always requires interpretation."[72] In the committee's discussions, responses to the above questions and similar issues varied among and within the specialty groups constituting the committee and reviewers.

Differences in risk tolerance also exist between parents and physicians and may exist among family members. A clinician may estimate that an infant's risk of meningitis is 1% and an LP is indicated, whereas a parent may have a higher threshold for consenting to the procedure. These differences, along with other parent beliefs and values, provide further challenges in an effort to share decision-making in an acute setting.

CONSENSUS RECOMMENDATIONS

The recommendations in this guideline reflect universal agreement or a strong consensus among committee members. In the one situation when there was majority but not consensus agreement, additional committee members were appointed and added; subsequently, consensus was achieved. The major reason for disagreement was varying levels of risk tolerance among committee members. For these recommendations, a more detailed explanation of the uncertainties involved and attempts to derive numbers needed to test and numbers needed to treat are provided in the specific Key Action Statements.

METHODOLOGY

The working group consisted of representatives from epidemiology; general pediatrics; pediatric subspecialties, including emergency medicine, infectious diseases, and hospital medicine; and family medicine. Individuals with expertise in guideline development, algorithm creation, and quality improvement were also included. During the development of this guideline, all members had access to the AHRQ evidence review,[26] the additional analyses by the committee epidemiologist (C.R.W. Jr.) as well as others, copies of all published literature cited in these reports, and the opportunity to participate in 4 meetings convened at the AAP and on conference calls. The authoring group relied on data and analyses from the following: (1) a formal analysis and systematic review of published articles from the United States and selected international countries that was conducted by an Evidence-Based Practice Center under contract to AHRQ; (2) a supplemental review and analyses were performed by the epidemiologist assigned to the committee; (3) consistent with a previous AAP guideline[73] if literature gaps existed, data were solicited and received from authors of previously published, peer-reviewed articles who performed additional analyses from their investigations: Kaiser Permanente Northern California; Intermountain Healthcare; the AAP PROS network; the Febrile Young Infant Research Collaborative (FYIRC); Boston Children's Hospital; The European Collaborative Group; Cruces University Hospital, Barakaldo, Spain; and the PECARN; and (4) committee members with active research and data collection projects provided ongoing study reports. Ongoing data analyses from these works in progress are consistent with cited references and support the recommendations.

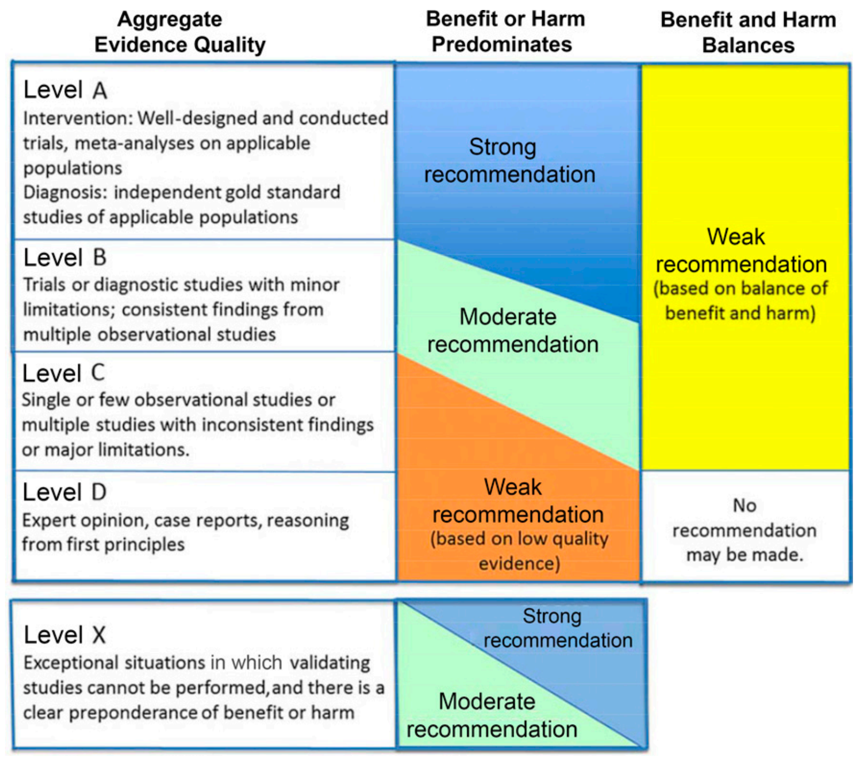

FIGURE 5 AAP rating of evidence and recommendations.

Finally, after the formulation of a set of recommendations, there was further consideration by AAP Sections and Committees, external organizations, physician reviewers, and parents, as well as focus groups of pediatricians from general pediatrics, pediatric hospital medicine, pediatric emergency medicine, pediatric critical care, and pediatric infectious diseases (see Acknowledgments for review groups).

The committee's focus was to develop a guideline to improve the diagnosis and treatment of UTIs, bacteremia, and meningitis. Sometimes the term "SBI" is used because it was the only outcome measure reported in many investigations. In some analyses, bacteremia and bacterial meningitis are combined as IBIs because of the nature of those infections compared with UTIs.

Recommendations are contained in the algorithms for infants 8 to 21 days of age, 22 to 28 days of age, and 29 to 60 days of age and are expounded in the accompanying Key Action Statements. For each recommendation, the quality of available evidence on which the recommendation is based is rated, and the strength of each recommendation is provided (Fig 5). Risks and benefits also are indicated, and assessments of their balance are provided.

In accordance with recent suggestions by the National Academy of Medicine, the committee attempted transparency by occasionally commenting on value judgments.[74] A clinical decision involves more than just knowing a specific risk. The decision about what action is appropriate with a given risk depends on the experience, value judgments, and risk tolerance and aversion of the interpreting clinician. To the extent possible, it is appropriate to incorporate parents' values and preferences in shared decision-making.

As noted above and consistent with all AAP clinical practice guidelines, each recommendation represents a consensus of the committee, although not necessarily universal agreement.

POPULATION ADDRESSED

This guideline addresses febrile infants who are well appearing. Infants appearing moderately or severely ill are at higher risk for IBIs and are NOT addressed in the guideline. Because of the difficulties assessing well appearance discussed previously in Challenges, we recommend that when clinicians are uncertain as to whether an infant is well appearing, this guideline should not be applied.

For eligibility, this guideline addresses febrile infants who (1) are well appearing, (2) have documented rectal temperatures of ≥38.0°C or 100.4°F at home in the past 24 hours or determined in a clinical setting, (3) had a gestation between ≥37 and <42 weeks, and (4) are 8 to 60 days of age and at home after discharge from a newborn nursery or born at home.

The following merit additional consideration specific to their condition and are intended to be excluded from the algorithms:

1. Preterm infants (<37 weeks' gestation).
2. Infants younger than 2 weeks of age whose perinatal courses were complicated by maternal fever, infection, and/or antimicrobial use.
3. Febrile infants with high suspicion of herpes simplex virus (HSV) infection (eg, vesicles).
4. Infants with a focal bacterial infection (eg, cellulitis, omphalitis, septic arthritis, osteomyelitis). These infections should be managed according to accepted standards.
5. Infants with clinical bronchiolitis, with or without positive test results for respiratory syncytial virus (RSV). A review by Ralston et al of 11 studies of bronchiolitis found no cases of meningitis, and researchers in 8 studies reported no cases of bacteremia.[51]
6. Infants with documented or suspected immune compromise.
7. Infants whose neonatal course was complicated by surgery or infection.
8. Infants with congenital or chromosomal abnormalities.
9. Medically fragile infants requiring some form of technology or ongoing therapeutic intervention to sustain life.
10. Infants who have received immunizations within the last 48 hours. The incidence of postimmunization fevers ≥38.0°C is estimated to be >40% within the first 48 hours.[75]

Infants with the following may be included:

1. Respiratory symptoms: the presence of upper respiratory tract infection symptoms or other respiratory symptoms not diagnostic of bronchiolitis should not exclude infants from inclusion in the pathway.
2. Diarrhea: infants suspected of having diarrhea caused by treatable bacterial pathogens should have stool specimens tested. If studies for bacteria are negative, infants may then enter the decision tree pathway. Loose stools do not exclude infants from the pathway.
3. Otitis media: diagnosing infants with presumed otitis media does not preclude their entry into the pathway.
4. Current or recent use of antimicrobial agents in infants older than 2 weeks of age requires individualized interpretation for febrile infants who enter the pathway.
5. Positive viral test results: the availability of rapid respiratory molecular testing for a variety of viruses is increasing, outpacing the availability of evidence for how such testing should be used.

The 2014 Cochrane review that included older infants and children did not recommend respiratory viral testing in the ED.[52] In evaluating the implications of a positive viral respiratory test result, numerous studies have documented lowering of IBI risk in subsets of patients. However, no prospective study has yet provided convincing data on whether a positive viral test result sufficiently reduces the IBI risk to change decision-making, after considering other historical, clinical, and available markers of inflammation.

In a 2004 study, Byington et al evaluated whether a positive respiratory viral test result lowered the risk of IBI in 1385 infants 1 to 90 days of age.[76] Viruses were detected in 35%, and the bacteremia risk in the viral-positive infants was 1%, significantly lower than the 2.7% in viral-negative infants. When positive viral test results were combined with the Rochester classification, there was no reduction in risk for infants already classified as low risk. Rochester high-risk group infants with positive viral test results had a similar prevalence of bacteremia as low-risk infants.

Emerging data from several large studies address viral testing in young febrile infants stratified by age. Infants <28 days of age with a positive viral test result have a risk of IBI from 1.1% to 2.1%.[44–50,76] One

TABLE 1 Summary of Key Action Statements

	Evidence Quality; Strength of Recommendation
Infants 8 to 21 d of age (KASs 1-7): Clinicians …	
KAS 1: Should obtain urine specimen by catheterization or suprapubic aspiration (SPA) of bladder for urinalysis and, if urinalysis result is positive, for culture.	Grade: A; Strong Recommendation
KAS 2: Should obtain a blood culture.	Grade: A; Strong Recommendation
KAS 3: May assess IMs.	Grade: B; Weak Recommendation
KAS 4: Should obtain CSF for analysis (WBC count, protein, glucose, Gram stain) and culture for bacteria. See notes for viral testing.	Grade: A; Strong Recommendation
KAS 5: Should initiate parenteral antimicrobial therapy.	Grade: A; Strong Recommendation
KAS 6: Should actively monitor infants while awaiting results of bacterial cultures in a hospital setting with nurses and staff experienced in the care of neonates/young infants.	Grade: B; Moderate Recommendation
KAS 7a: Should discontinue parenteral antimicrobial agents and discharge hospitalized patients when all of the following criteria are met: (1) culture results are negative for 24–36 h or only positive for contaminants; (2) the infant continues to appear clinically well or is improving (eg, fever, feeding); (3) there are no other reasons for hospitalization.	Grade: B; Strong Recommendation
KAS 7b: Should treat infants' positive bacterial pathogens in urine, blood, or CSF with targeted antimicrobial therapy for the duration of time consistent with the nature of the disease, responsible organism, and response of the infant to treatment.	Grade: A; Strong Recommendation
Infants 22 to 28 d of age (KASs 8–4): Clinicians …	
KAS 8: Should obtain urine specimen by catheterization or SPA of bladder for urinalysis and, if urinalysis result is positive, for culture.	Grade: A; Strong Recommendation
OR Should obtain urine specimen by bag, spontaneous void, or stimulated void for urinalysis and, if urinalysis result is positive, obtain a catheterization or SPA specimen for culture.	Grade: A Strong Recommendation
KAS 9: Should obtain a blood culture.	Grade: A; Strong Recommendation
KAS 10: Should assess IMs.	Grade: B; Strong Recommendation
KAS 11a: Clinicians may obtain a CSF analysis on infants 22–28 d of age even if all of the following criteria are met: (1) urinalysis result is negative or positive; (2) no IM obtained is abnormal; (3) blood and urine cultures have been obtained; (4) infant is hospitalized.	Grade: B; Moderate Recommendation
KAS 11b. Should obtain CSF for analysis (WBC count, protein, glucose, Gram stain), and bacterial culture if any IM obtained is abnormal.	Grade: C; Moderate Recommendation
KAS 12a. Should administer parenteral antimicrobial therapy in a hospital if either of the following apply: (1) CSF analysis suggests bacterial meningitis; (2) urinalysis result is positive.	Grade: A; Strong Recommendation
KAS 12b. May administer parenteral antimicrobial therapy in a hospital if ALL of the following apply: (1) CSF analysis is normal; (2) urinalysis is normal; (3) Any IM obtained is abnormal.	Grade: B; Moderate Recommendation
KAS 12c. May administer parenteral antimicrobial therapy to hospitalized infants even if ALL of the following are met: (1) urinalysis is normal; (2) no IM obtained is abnormal; (3) CSF analysis is normal or enterovirus-positive.	Grade: B; Weak Recommendation
KAS 12d: Should administer parenteral antimicrobial therapy for infants who will be managed at home even if ALL of the following are met: (1) urinalysis is normal; (2) No IM obtained is abnormal; (3) CSF analysis is normal.	Grade: C; Moderate Recommendation
KAS 13a: May manage infants at home if all of the following criteria are met: (1) Urinalysis is normal; (2) No IM obtained is abnormal. (3) CSF analysis is normal or enterovirus-positive. (4) Verbal teaching and written instructions have been provided for monitoring throughout the period of time at home. (5) Follow-up plans for reevaluation in 24 h have been developed and are in place. (6) 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.	Grade: B; Moderate Recommendation
KAS 13b: Should hospitalize infants in a facility with nurses and staff experienced in the care of neonates/young infants when CSF is not obtained or is uninterpretable.	Grade: B; Weak Recommendation
KAS 14a: Should discontinue antimicrobial agents and discharge hospitalized infants after 24 to 36 h of negative culture results if the following are met: (1) the infant is clinically well or improving (eg, fever, feeding); (2) there are no other reasons for hospitalization; (3) there is no other infection requiring treatment (eg, otitis media).	Grade: B; Strong Recommendation
KAS 14b: Should discontinue antimicrobial agents on infants managed at home when all of the following criteria are met: (1) infant is clinically well or improving (eg, fever, feeding) at time of reassessment; (2) all culture results are negative at 24–36 h; (3) there is no other infection requiring treatment (eg, otitis media).	Grade: B; Strong Recommendation
KAS 14c: Should treat infants' positive bacterial pathogens in urine, blood, or CSF with targeted antimicrobial therapy for the duration of time consistent with the nature of the disease, responsible organism, and response of the infant to treatment.	Grade: A; Strong Recommendation
Infants 29 to 60 d of age (KASs 15-21): Clinicians . . .	
KAS 15: Should obtain urine specimen by bag, spontaneous void, or stimulated void for urinalysis and, if urinalysis result is positive, obtain a catheterization or SPA specimen for culture.	Grade: A; Strong Recommendation
or Should obtain urine specimen by catheterization or SPA of bladder for urinalysis and, if result is positive, for culture.	Grade: A; Strong Recommendation

TABLE 1 Continued

	Evidence Quality; Strength of Recommendation
KAS 16: Should obtain a blood culture.	Grade: B; Moderate Recommendation
KAS 17: Should assess IMs.	Grade: B; Moderate Recommendation
KAS 18a: May obtain CSF for analysis (WBC count, differential, protein, glucose, Gram stain), culture for bacteria, and test for enterovirus when CSF pleocytosis is detected or during enterovirus season if any IM is abnormal.	Grade: C; Weak Recommendation
KAS 18b: Need not obtain CSF for analysis and culture if all IMs obtained are normal.	Grade: B; Moderate Recommendation
KAS 19a: Should use parenteral antimicrobial therapy if CSF analysis suggests bacterial meningitis.	Grade: A; Strong Recommendation
KAS 19b: May use parenteral antimicrobial therapy if both of the following apply: (1) CSF analysis (if CSF obtained) is normal; (2) any IM obtained is abnormal.	Grade: B; Moderate Recommendation
KAS 19c: Should initiate oral antimicrobial therapy if all of the following apply: (1) CSF analysis (if CSF obtained) is normal; (2) urinalysis result is positive; (3) no IM obtained is abnormal.	Grade: B; Strong Recommendation
KAS 19d: Need not use antimicrobial therapy while awaiting bacterial culture results if all of the following are met: (1) CSF analysis, if CSF obtained, is normal or enterovirus-positive; (2) urinalysis result is negative; (3) no IM obtained is abnormal.	Grade: B; Moderate Recommendation
KAS 20a: Should hospitalize infants in a unit with nurses and staff experienced in the care of 29- to 60-d-old infants if CSF analysis, if CSF obtained, is abnormal.	Grade: A; Strong recommendation
KAS 20b: May hospitalize infants in a unit with nurses and staff experienced in the care of 29- to 60-d-old infants if any IM obtained is abnormal.	Grade: B; Moderate recommendation
KAS 20c: Should manage patients at home if all of the following criteria are met: (1) CSF analysis, if CSF obtained, is normal; (2) urinalysis result is negative; (3) all IMs obtained are normal; (4) appropriate parental education has been provided; (5) follow-up plans for reevaluation in 24 h have been developed and are in place (6) 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.	Grade: B; Moderate Recommendation
KAS 20d: May manage infants without antimicrobial treatment at home without having obtained interpretable CSF if all of the following are met: (1) urinalysis result is negative; (2) all IMs obtained are normal; (3) parents can return promptly if there is a change in infant condition and agree to follow-up in 24 to 36 h. Infants monitored at home should be reassessed in the following 24 h.	Grade: B; Moderate Recommendation
KAS 21a. Should discontinue antimicrobial agents when all of the following are met: (1) all bacterial culture results are negative at 24–36 h; (2) infant is clinically well or improving (eg, fever, feeding); (3) there is no other infection requiring treatment (eg, otitis media).	Grade: B; Strong Recommendation
KAS 21b: Should discharge hospitalized patients with positive urine culture (UTI) results if all of the following are met: (1) blood culture result is negative; (2) result of CSF culture, if obtained, is negative; (3) infant is clinically well or improving (eg, fever, feeding); (4) there are no other reasons for hospitalization.	Grade: B; Strong Recommendation
KAS 21c: Should discontinue parenteral antibiotics (if started) and begin or continue oral antimicrobial for infants with UTIs managed at home when all of the following are met: (1) urine culture result is positive; (2) all other bacterial culture results are negative at 24–36 h; (3) infant is clinically well or improving (eg, fever, feeding).	Grade: B; Strong Recommendation
KAS 21d: Should treat infants' positive bacterial pathogens in urine, blood, or CSF with targeted antimicrobial therapy for the duration of time consistent with the nature of the disease, responsible organism, and response of the infant to treatment.	Grade: A; Strong Recommendation

study found statistically significant reductions in the prevalence of IBI when compared with viral-negative infants.[50] Other studies revealed lower rates of IBI but not statistically significantly lower.[44,47,48] In a prospective PECARN study for infants <28 days of age, bacteremia was detected in 1.1% and meningitis in 0.8% of infants with detected viral infections.[48] The risks of IBI in viral-positive infants <28 days of age are sufficiently high to warrant similar testing and treatment as viral-negative infants.

For infants 29 to 60 days of age, the bacteremia rate was significantly lower in viral-positive infants compared with viral-negative infants (0.6% vs 1.8%).[48] Another recent study of 29- to 90-day old infants detected bacteremia in 3.7% of viral-negative infants, whereas those with rhinovirus infections had a prevalence of 1.4% and a reduced relative risk of 0.52 (95% confidence interval [CI], 0.34–0.81).[50] There are situations in which viral testing may augment the recommended evaluation and management of febrile infants 29 days and older, such as during RSV, bronchiolitis,[51] or influenza seasonal outbreaks. In these situations, individual tests for RSV or influenza can each be obtained at <3% the cost of a multiplex respiratory viral panel, according to the latest charges listed in *Current Procedural Terminology*; the cost of multiplex testing in other countries has been reported to be substantially lower. In

KAS 1: Clinicians should obtain urine specimen by catheterization or SPA of bladder for urinalysis and, if urinalysis result is positive, for culture. Evidence Quality: A; Strong Recommendation

Benefits	Identification of UTIs Basing culture on urinalysis results reduces likelihood of false-positive result attributable to contamination or misdiagnosis of asymptomatic bacteriuria.
Risks, harm, cost	Requiring positive urinalysis result may miss some true UTIs. Obtaining culture if negative urinalysis result may result in falsely positive culture attributable to contamination or misdiagnosis of asymptomatic bacteriuria leading to inaccurate documentation of a first UTI (which may prompt unnecessary imaging should a UTI occur subsequently). Discomfort of catheterization or SPA. Parent anxiety.
Benefit–harm assessment	Preponderance of benefit based on high rate of UTI.
Shared decision-making	Parents opposed to catheterization should be offered a choice of SPA and informed about the higher rate of ambiguous/false-positive culture results obtained from bagged or voided specimens.[77,78]
Key references	73, 77–93

summary, although viral testing should not affect entrance into the recommended pathway, for infants >28 days of age, it can be considered in individualizing evaluation and management decisions.

Summary of KASs for Evaluation and Management of Well-Appearing Febrile Infants: 8 to 21, 22 to 28, and 29 to 60 Days of Age (Table 1)

WELL-APPEARING 8- TO 21-DAY-OLD INFANTS

Diagnostic Evaluation

The following recommendations and options are for febrile (temperature ≥38.0°C), well-appearing, term infants 8 to 21 days of age without risk factors identified in the exclusion criteria.

KAS 1: Clinicians should obtain urine specimen by catheterization or SPA of bladder for urinalysis and, if urinalysis result is positive, for culture. Evidence Quality: A; Strong Recommendation

A positive urinalysis result for purposes of this guideline is defined as the presence of any leukocyte esterase (LE) on dipstick, >5 WBCs per high-powered field (hpf) in centrifuged urine, or >10 WBCs/mm^3 in uncentrifuged urine on microscopic urinalysis using a hemocytometer.

Urinalysis: Of the estimated 10% of febrile infants with UTIs, 94% have urinalysis positive for leukocyte esterase (LE) (95% CI, 91%– to 97%).[80] The sensitivity is even higher for UTI associated with bacteremia (97.6% and 100% in 2 studies).[80,86] Therefore, for 1000 infants, ~approximately 94 to 98 infants with UTIs will be detected by a positive urinalysis result, and 2 to 6 may be “missed.” It is unclear whether a “miss” represents a UTI, asymptomatic bacteriuria, or contamination. Consequently, if a urinalysis result is negative, an estimated 200 to 500 catheterizations or suprapubic aspirations (SPAs) followed by cultures would be required to detect 1 additional infant with bacteriuria, and that infant might have asymptomatic bacteriuria or contamination rather than a true UTI.

Culture: In the AAP clinical practice guideline on UTI from 2011, reaffirmed in 2016, addressing infants 2 to 24 months of age, the diagnosis of UTI was made on the basis of pyuria and at least 50 000 colony-forming units (cfu) per mL of a single uropathogenic organism in an appropriately collected specimen of urine.[73] Recent studies indicate it

KAS 2: Clinicians should obtain a blood culture. Evidence Quality: A; Strong Recommendation

Benefits	Identification of bacteremia: 3.9% to 5.1% of all febrile infants in this age group[17,24,61,94]; 15% to 20% of infants younger than 28 d with UTI.[91,93,94] Identification of organism (and sensitivities) for directed antimicrobial treatment. Early detection and treatment may prevent progression of infection.
Risks, harm, cost	False-positive results: Most positive blood cultures in febrile infants are attributable to contaminants (63% to 88%),[25,27,30] potentially leading to unnecessary use of antimicrobial agents, further or repeat testing, and prolonged hospitalization. Discomfort of venipuncture. Costs can be substantial depending on further testing, treatment, and hospitalization after a false-positive culture result.
Benefit–harm assessment	Preponderance of benefit.
Shared decision-making	Parents can be made aware that testing is based on the high likelihood of bacteremia, especially in infants with a positive urinalysis result. Parents can be informed of potential challenges that may be encountered in distinguishing pathogens from contaminants as part of explaining the evaluation process.
Key references	27,61,93

KAS 3: Clinicians may assess IMs. Evidence Quality: B; Weak Recommendation

Benefits	For infants with negative urinalysis and negative CSF analysis results, abnormal IM results may influence decisions regarding when to discontinue antimicrobial therapy and hospitalization in infants with negative culture results.
Risks, harm, cost	False-negative results, underestimating risk of bacteremia or bacterial meningitis with normal IMs.[16,27,39] False-positive results, overestimating the risk of bacteremia or bacterial meningitis. Adds additional, marginal cost as it is recommended all infants in this age group will be hospitalized.
Benefit–harm assessment	Balance of benefit and harm.
Key references	18–20, 39, 60, 107

A detailed discussion of IMs follows KAS 10.[95–105]

is reasonable to extend the recommendation of the AAP UTI guideline to infants addressed here,[77–80,85–89] although 10 000 colony-forming units/mL is now an acceptable threshold for diagnosing UTI from catheterized urine specimens when pyuria and fever are also present.[80,89] This new level also circumvents the problem of interpreting data from laboratories not reporting gradations from 10 000 to 100 000. Positive urine culture results obtained in the absence of an abnormal urinalysis indicating inflammation are likely to represent asymptomatic bacteriuria or contamination.

Culture of urine specimens not collected by catheterization or SPA is not recommended because of an unacceptable rate of false-positive results attributable to contamination of such specimens.[77,78] An initial urine specimen obtained by catheter or SPA obviates the delay and need for a second specimen by catheter or SPA following after a positive result from a bag urine. The sensitivity and specificity of urinalysis parameters for UTI from bagged specimens are somewhat less than those of catheterized specimens.[77,78]

For physicians with experience, SPA is effective, provides the "cleanest" specimen, and saves time; complications are rare.[81] In some situations, such as phimosis or labial adhesions, SPA may be required[73]; a training video is available online.[82]

KAS 2: Clinicians should obtain a blood culture. Evidence Quality: A; Strong Recommendation

KAS 3: Clinicians may assess IMs. Evidence Quality: B; Weak Recommendation

Because it is recommended that all 8- to 21-day-old infants be hospitalized and treated, IMs are not required for these initial decisions. However, some clinicians consider them useful in decision-making about later management, such as whether to discontinue antimicrobial agents at 24 or 36 hours while awaiting final results of bacterial cultures.

KAS 4: Clinicians should obtain CSF for analysis (WBC count, protein, glucose, Gram stain), and culture for bacteria. See notes for viral testing. Evidence Quality: A; Strong Recommendation.

CSF with pleocytosis or from infants with HSV risk factors should be evaluated for HSV.[116,117] Population-based rates of HSV in neonates range from 2 to 5 per 100 000, with 15% having fever as the only symptom.[108–116] Although rare in well-appearing infants, prompt recognition and treatment of HSV in infants, especially those younger than 21 days with other risk factors, is essential. In addition to the presence of vesicles and/or seizures, infants should be

KAS 4: Clinicians should obtain CSF for analysis (WBC count, protein, glucose, Gram stain), and culture for bacteria. See notes for viral testing. Evidence Quality: A; Strong Recommendation

Benefits	Early detection of bacterial meningitis. The prevalence of meningitis is 0.5%–1.3% in this age group.[24,94] Detection of CSF pleocytosis or elevated protein attributable to HSV infection. Early treatment may decrease neurologic morbidity. Identification of pathogen from CSF to target type and duration of antimicrobial treatment. A normal CSF analysis helps in the decision whether to discharge infants at 24 to 36 h. Avoids unnecessarily prolonged antimicrobial therapy if CSF was obtained after antimicrobial agents started and diagnosis of meningitis is uncertain.
Risks, harm, cost	Discomfort for infant. Potential for transient respiratory compromise during positioning for LP. Traumatic LPs yielding uninterpretable CSFs have been documented to prolong length of stay for hospitalized infants. False-positive CSF culture results[27,106,107] prolonging hospitalization. Substantial cost if hospitalizing because of ambiguous CSF or prolonged hospitalization for bacterial contaminant. Parental anxiety.
Benefit–harm assessment	Preponderance of benefit.
Shared decision-making	Parents must consent to this procedure. If, for whatever reason, a parent is resistant or unwilling to consent to an LP, the risk of meningitis, the evidence quality, benefit/harm assessment, and value judgments should be communicated to the parent to foster informed decision-making. The potential need for a future LP, depending on further clinical information and progress, is an important part of the discussion. These discussions should be documented.
Key references	66–70, 108, 111, 137

considered at increased risk of HSV if any of the following are present: CSF pleocytosis with a negative Gram stain, leukopenia, thrombocytopenia, hypothermia, mucous membrane ulcers, or maternal history of genital HSV lesions or fever from 48 hours before to 48 hours after delivery. If liver function tests were obtained, an elevated alanine aminotransferase (ALT) also indicates a higher risk of HSV. For further details of evaluation and management of HSV, see the AAP *Red Book*.[111]

Enterovirus (EV) PCR testing should be performed on CSF with pleocytosis and during months when there is a seasonal increase in enterovirus, regardless of pleocytosis. Rapid detection of enterovirus, along with HSV and an emerging viral cause of meningitis, human parechovirus (HPeV), can be accomplished with meningoencephalitis multiplex PCR panels identifying 14 pathogens.[43,118,119] When available in a timely fashion, multiplex PCR testing can enhance clinical decision-making.

Pleocytosis is detected overall in 8.8% of CSF analyses; the rate is higher in summer (17%) because of enterovirus.[117] The likelihood of bacterial meningitis in the presence of enterovirus in the CSF is low.[120] Therefore, the detection of CSF enterovirus can eliminate the need for further interventions.[121,122] Newer tests provide rapid identification of enterovirus.[123,124] CSF pleocytosis is often detected in febrile infants with UTIs who do not have bacterial, enterovirus or HSV meningitis.[126–128] These panels can give rapid results but should only be used as an addition to bacterial cultures. There are still relatively limited data on young infants so precise test accuracy is still uncertain, and there have been reports of both false-positive and false-negative results; *Listeria* is not in the panel.[118,119]

KAS 5: Clinicians should initiate parenteral antimicrobial therapy. Evidence Quality: A; Strong Recommendation

Benefits	Anticipated reduction in morbidity and mortality from bacterial infections.
Risks, harm, cost	Adverse drug reactions including anaphylaxis (rare). Complications related to intravenous lines including infiltration, infection, nerve compression (in ankle). Potential disruption of evolving microbiome. Development of antimicrobial resistance.
Benefit–harm assessment	Preponderance of benefit.
Key references	15, 17–20, 25, 27, 30, 145

An LP is not always successful. The rate of failure and/or traumatic LP in infants younger than 90 days is 20% to 50%; the rate of unsuccessful or dry LP is 25% to 40%; the rate of bloody LP is 10% to 30%.[106,130–132] Ultrasonography may assist in obtaining CSF.[133] When using a bedside ultrasound landmark-guided technique, success in obtaining CSF on the first LP attempt was 58% compared with 31% without ultrasonography. Using ultrasonography resulted in a 75% success rate after 3 attempts.[135]

There is also a significant rate of nonpathogenic bacteria cultured from CSF. In a multisite study with 410 positive CSF bacterial culture results in infants <90 days of age, researchers found only 13% were pathogens and the rest were contaminants.[107] Authors of another study from Kaiser Permanente Northern California found only 22% of CSF isolates from infants <90 days to be pathogens.[27] Authors in a study of febrile infants in the second month of life found that 40 of 41 positive culture results were caused by contaminants.[106]

The CSF from a traumatic LP should be cultured and can be tested for HSV if indicated. In general, correction (or ratios) for red blood cells (RBCs) in CSF is discouraged because of lack of validating studies. It is reasonable to interpret CSF WBC counts at face value in CSF specimens with up to 10 000 RBCs per mm^3 (Table 2).[133]

INITIAL TREATMENT

The antimicrobial agents in Table 3 are recommended for initial empirical therapy and should be modified following results of cultures and sensitivities.

TABLE 2 CSF Values in Febrile Infants Without Evidence of UTI, IBI, HSV, Enterovirus, or Traumatic CSF

	Age, d	*n*	Mean	Median	Range
WBCs per mm^3	1–28	278	6.1	5.0	0–18
	29–60	318	3.1	3.0	0–8.5
Protein mg/dL	1–28	278	75.4	73.0	15.8–131.0
	29–60	318	58.9	54.0	5.5–105.5
Glucose	1–28	278	45.3	46.0	30.0–61.0
Glucose	29–60	318	48.0	48.0	20.6–65.5
RBCs per mm^3	1–28	278	95.5	5.5	0–236
RBCs per mm^3	29–60	318	75.5	2.0	0–64.5

Statistical outliers were removed. Other studies reveal slightly different ranges. Local laboratory tests may provide slightly different upper limits of normal. Adapted from Byington CL, Kendrick J, Sheng X. Normative cerebrospinal fluid profiles in febrile infants. *J Pediatr.* 2011;158(1):130–134.

KAS 6: Clinicians should actively monitor infants while awaiting results of bacterial cultures in a hospital setting with nurses and staff experienced in the care of neonates and young infants. Evidence Quality: B; Moderate Recommendation

Benefits	Hospitalization allows ongoing monitoring for a change in clinical status and the ability to change management and/or expeditiously transfer to a more intensively monitored unit if required. Relieves parents of monitoring responsibility and may reduce anxiety. Provides ability to administer intravenous antimicrobial agents.
Risks, harm, cost	Hospitalization increases risk of hospital-acquired infections. Increased risk of iatrogenic events related to intravenous catheters. Parental anxiety about infant's condition and financial strain. Stress to mothers because of breastfeeding challenges and separation from other children. Substantial cost.
Benefit–harm assessment	Preponderance of benefit.
Shared decision-making	Although monitoring in a hospital is recommended, parents have the right to refuse. Risks and consequences of IBI and of hospitalization should be discussed. In the event parents choose to return home, parents should understand criteria for returning to the hospital discussed in KAS 13.
Key references	57, 68–70, 136

KAS 5: Clinicians should initiate parenteral antimicrobial therapy. Evidence Quality: A; Strong Recommendation

The recommendation to treat all infants 8 to 21 d of age is based on the prevalence of IBIs being highest in this age category (Fig 4) and ~2% (number needed to treat 50) even in infants with negative urinalysis and or IMs. The preponderance of evidence indicates that infants with viral infections have a risk of IBI of ~1% or a number needed to treat of 100. See above discussion.

Overall, for studies since the year 2000 in infants <90 days of age, Gram-negative organisms have been responsible for the majority of infections (60% to 80%). *E coli* has been the most common pathogen detected, with a prevalence of 70% to 90% of UTIs, 30% to 60% of bacteremia infections, and 15% to 30% of bacterial meningitis.[17,26,31,39,61,94] The prevalence of GBS infection in the first week of life has declined because of prenatal screening and peripartum antimicrobial prophylaxis but is still encountered in >20% of febrile infants with bacteremia after the first week. In a 2013 series, GBS was the most common pathogen in the second month[30] and was the most common cause of meningitis in the 2019 Reducing Variability in the Infant Sepsis Evaluation study.[31] *L monocytogenes* is rarely encountered.[29–33]

Enteroviral testing of CSF has been shown to shorten length of stay and duration of antimicrobial use.[120,137] It is helpful if available within a time period that will assist clinical decision-making. In general, if CSF is positive for enterovirus, antimicrobial agents should be discontinued (or withheld), because concomitant enteroviral and bacterial meningitis is rare. However, in some cases of enterovirus meningitis or meningoencephalitis, CSF may reveal a significant pleocytosis with a neutrophil predominance. In such cases, or in cases in which there is otherwise reason to suspect a concomitant bacterial infection, such as abnormal IMs, it is reasonable to continue antimicrobial agents until CSF and blood cultures are negative for 24 to 36 hours.

In communities with circulation of *E coli* strains that produce extended-spectrum β-lactamases, gentamicin should be used instead of ceftazidime for treatment of suspected bacteremia or sepsis, and meropenem should be used

KAS 7a: Clinicians should discontinue parenteral antimicrobial agents and discharge hospitalized patients when all of the following criteria are met: (1) culture results are negative for 24–36 h or only positive for contaminants; (2) the infant continues to appear clinically well or is improving (eg, fever, feeding); and (3) there are no other reasons for hospitalization. Evidence Quality: B; Strong Recommendation

Benefits	Discontinuing antimicrobial agents minimizes risk of adverse treatment consequence. Reduces impact on microbiome. Contributes to antimicrobial stewardship. Discharge minimizes exposure to nosocomial infections and iatrogenic exposures. Limits family disruption. Reduces cost of illness episode.
Risks, harm, cost	Inadequate duration of therapy with antimicrobial (if treated) for bacterial pathogen not identified before discontinuation. Potential clinical deterioration at home if inadequate treatment of pathogen not detected before discharge.
Benefit–harm assessment	Preponderance of benefit.
Shared decision-making	Parents should be made aware of the low risk of undetected pathogens after 24 to 36 h and be able to return in a timely fashion for: Change in general appearance particularly a dusky color, or respiratory or other distress; Behavior change, including lethargy, irritability, inconsolable crying, difficulty in consoling or comforting, or other evidence of distress; Difficulty feeding; Vomiting; Decreased urine output.
Key references	57, 107, 138–144

KAS 7b: Clinicians should treat infants' positive bacterial pathogens in urine, blood, or CSF with targeted antimicrobial therapy for the duration of time consistent with the nature of the disease, responsible organism, and response of the infant to treatment. Evidence Quality: A; Strong Recommendation

Benefits	Treats infection. Reduces likelihood of morbidity. Contributes to antimicrobial stewardship.
Risks, harm, cost	Adverse reaction to antimicrobial. Interferes with infant's evolving microbiome. Accelerates emergence of antimicrobial resistance.
Benefit–harm assessment	Preponderance of benefit.
Key references	145

instead of ceftazidime when bacterial meningitis is suspected. Use of fourth- and fifth-generation cephalosporins may also be considered with expert consultation.

Cephalosporins do not provide adequate coverage for *Listeria* or enterococci. Ampicillin generally should be used as part of empirical therapy when these microbes are suspected.

FURTHER MANAGEMENT AND MONITORING

KAS 6: Clinicians should actively monitor infants while awaiting results of bacterial cultures in a hospital setting with nurses and staff experienced in the care of neonates and young infants. Evidence Quality: B; Moderate Recommendation

The committee recommends that, to improve the care of hospitalized infants, efforts should be directed at optimizing the environment to support maternal/child bonding and breastfeeding. This can be accomplished through the following effective measures: allow parents to room-in with the infant; encourage the continuation of breastfeeding and provide lactation support including access to breast pumps for nursing mothers; provide timely communication with families about the results and interpretation of testing and expected consequences of having a diagnosis of UTI, bacteremia, and/or bacterial meningitis on the basis of ongoing results; provide timely communication with the infant's primary care provider.

KAS 7a: Clinicians should discontinue parenteral antimicrobial agents and discharge hospitalized patients when all of the following criteria are met:

1. **culture results are negative for 24 to 36 hours or only positive for contaminants;**
2. **the infant continues to appear clinically well or is improving (eg, fever, feeding); and**
3. **there are no other reasons for hospitalization.**

Evidence Quality: B; Strong Recommendation

Although infants whose CSF is positive for enterovirus may be observed without antimicrobial agents, they should remain in a hospital setting for a minimum of 24 h because of the small risk of progression to enteroviral sepsis, which generally only occurs in infants <21 d of age.

Discontinuation of antimicrobial agents and discharge at 36 hours can potentially result in a lapse of treatment of a slow-growing pathogen and readmission, but this has seldom been reported. Automated blood culture techniques and multiplex PCR detection have reduced the time to identify pathogens.[40–42] Time to positivity of blood culture is dependent on the type and concentration of bacterial organism. Between 4% and 17.6% of pathogens take >24 hours to grow; less than 5% take >36 hours.[138–144] Compared with ill-appearing infants, infants not appearing ill are less likely to have pathogens identified in <24 hours (85.0% vs 92.9%). Pathogens vary in median times to positivity: GBS takes 9.3–14.3 hours[138–140,143]; *E coli* takes 11.3–13.6 hours[138,140,143]; and *S aureus* takes 18.5–19.9 hours.[138–140,143] For *E coli*, the most common organism identified, 24% take longer than 24 hours to grow, whereas only 5.9% of GBS grow after 24 hours.[138]

KAS 8: Clinicians should obtain urine specimen by catheterization or SPA of bladder for urinalysis and, if urinalysis result is positive, for culture, or should obtain urine specimen by bag, spontaneous void, or stimulated void for urinalysis and, if urinalysis is positive, obtain a catheterization or SPA specimen for culture. Evidence Quality: A; Strong Recommendation

Benefits	Identification of UTIs.
Risks, harm, cost	Falsely positive culture result (contamination) or misdiagnosis of asymptomatic bacteriuria leading to unnecessary and potentially harmful treatment and inaccurate documentation of a first UTI (which may prompt unnecessary imaging should a UTI occur subsequently). Discomfort of catheterization or SPA. Parent anxiety.
Benefit–harm assessment	Preponderance of benefit.
Role of parent preferences	Parents opposed to catheterization should be offered a choice of SPA and informed about the higher rate of ambiguous or false-positive culture results obtained from bagged or voided specimens.[77,78] A false-positive urine culture result can potentially prolong antimicrobial administration and duration of hospitalization.
Key references	73, 77, 93

For detailed discussion, see KAS 1.

KAS 9: Clinicians should obtain blood culture. Evidence Quality: A; Strong Recommendation

Benefits	Identification of bacteremia: 1.6% to 5% of all febrile infants in this age group[17,24,61,94]; 7.5% to 10% of infants with UTI.[10,26,91–93] Identification of organism (and sensitivities) for targeted antimicrobial treatment. Early detection and treatment may prevent progression of infection.
Risks, harm, cost	False-positive results: most positive blood cultures in febrile infants are attributable to contaminants,[23,27,30] potentially leading to unnecessary use of antimicrobial agents, further or repeat testing, and prolonged hospitalization. Discomfort of venipuncture. Costs can be substantial depending on further testing, treatment, and/or hospitalization after a false-positive culture result.
Benefit–harm assessment	Preponderance of benefit.
Key references	27, 30, 61

Nonpathogens generally take longer than 24 hours to grow in culture media. Approximately 25% of nonpathogens grow in the first 24 hours.[138] Antimicrobials can be stopped at 24 hours if a pure growth of a nonpathogen is identified. When available, multiplex PCR is capable of detecting many bacterial pathogens and antimicrobial resistance from a positive culture medium in an hour.[40–43]

KAS 7b: Clinicians should treat infants' positive bacterial pathogens in urine, blood, or CSF with targeted antimicrobial therapy for the duration of time consistent with the nature of the disease, responsible organism, and response of the infant to treatment. Evidence Quality: A; Strong Recommendation

WELL-APPEARING 22- TO 28-DAY-OLD INFANTS

The following recommendations and options are for febrile (temperature >38.0°C), well-appearing, term infants 22 to 28 days old without risk factors identified in the exclusion criteria.

The evidence indicates the risk of bacteremia and bacterial meningitis is lower in infants 22 to 28 days of age than in infants 8 to 21 days of age. However, they continue to be at higher risk than older infants, leading us to separate this group as discussed above in the section on "Evidence for Age-based Risk Stratification."

Diagnostic Evaluation

KAS 8: Clinicians should obtain urine specimen by catheterization or SPA of bladder for urinalysis and, if urinalysis result is positive, for culture, or should obtain urine specimen by bag, spontaneous void, or stimulated void for urinalysis and, if urinalysis is positive, obtain a catheterization or SPA specimen for culture. Evidence Quality: A; Strong Recommendation

KAS 9: Clinicians should obtain blood culture. Evidence Quality: A; Strong Recommendation

KAS 10: Clinicians should assess IMs. Evidence Quality: B; Strong Recommendation

IMs have been included in every strategy proposed to address febrile infants. No single IM, in isolation, is reliable for risk stratification. Further study will allow ongoing accumulation of evidence and more precise values for these markers. The committee anticipates modification and refinement as efforts to improve the care of febrile infants continue.

- Temperature >38.5°C: A sign of inflammation, fever is the most readily available marker of infection. Surprisingly, it was not included in early studies of decision models,[10–15] but there has been ongoing and recent work on the value of fever elevation in predicting IBI.[16,17,48,57,60,95,96,147] It emerged as an important predictor in studies using recursive partitioning analysis to derive threshold fever values for prediction rules.[16,17] In the PROS Network study of 3066 infants with 63 cases of IBI, a temperature >38.5°C, when combined with ill appearance and age <25 days, had a sensitivity of 93.7% and NPV of 99.6%.[17] A temperature ≥38.5°C at any point during the ED stay placed infants at higher risk in a study of 207 cases of IBI in well-appearing febrile infants ≤60 days seen in the EDs of 11 children's hospitals in the Febrile Young Infant Research Collaborative.[60] Researchers in a PECARN analysis addressing SBI documented an increased in adjusted odds ratio of 1.8 for each 1°C increase >38.0.[48] Also, a temperature <38.5°C is used in

KAS 10: Clinicians should assess IMs. Evidence Quality: B; Strong Recommendation

Benefits	For infants with negative urinalysis and/or pending urine results and/or blood and/or CSF cultures, IMs may influence the decision whether to initiate antimicrobial agents. For an infant with a negative urinalysis result and pending blood culture result, the absence of abnormal IMs may contribute to the decision of whether to perform LPs in infants 22 to 28 d of age. In the presence of a negative CSF analysis or bloody or failed LP, normal IMs may influence decisions regarding hospitalization, initiation of antimicrobial agents, and duration of treatment.
Risks, harm, cost	False-negative results, underestimating risk of bacteremia or bacterial meningitis with normal IMs. False-positive results, overestimating the risk of bacteremia and bacterial meningitis (see discussion below).
Benefit–harm assessment	Preponderance of benefit.
Key references	13–16, 18–20, 37–39, 60, 97–105, 146

For purposes of this guideline, IMs are considered abnormal at the following levels: temperature >38.5°C, ANC >4000, 5200 per mm^3, CRP >20 mg/L, procalcitonin >0.5 ng/mL.

Intermountain Healthcare's Care Process Model to distinguish whether there is a need for further testing in infants older than 28 days who test positive for RSV.[57] Recently, by adding a temperature >38.5°C as an additional high-risk criterion to the Rochester criteria in 7- to 28-day-old infants, the Roseville Protocol documented a sensitivity of 96.7%.[147] Therefore, moderately elevated temperatures are useful in predicting IBI and can immediately suggest how extensive an evaluation may be appropriate. However, as an independent predictor, 30% of febrile infants with IBI have maximum documented fevers of ≤38.5.[96] Temperature elevation is a useful predictor of IBI when combined with other clinical features, and laboratory-based IMs can improve the sensitivity for detecting IBI.

- Elevated WBC count and its components: These tests are widely available, but with an evolving epidemiology of IBI and availability of newer tests, their usefulness in predicting IBIs is changing. The arbitrary thresholds (WBC count >15 000 per mm^3, ANC >10 000 per mm^3, band count >1500 per mm^3, immature to total neutrophil ratio >0.2) that define "abnormal" have been used in numerous studies of predictive models.[10–15,19,20] These studies all used WBC count components in combination with other infant characteristics such as well appearance, or urinalysis results, to identify low-risk infants. Researchers who analyzed WBC count and/or ANC as independent predictors of IBI[16,39,103,104] have documented that as a stand-alone screen, neither is sufficiently sensitive nor specific, although ANC is substantially better than the WBC count. Researchers in an ED study of 5279 infants <90 days of age identified 68 infants with IBIs.[16] Using a derived multivariable prediction rule with recursive partitioning analysis, they found that there were 14 misclassified cases of bacteremia and 1 case of bacterial meningitis. Of these 15 infants, 9 had "normal" WBC counts (5000–15 000/mm^3). This study indicates that a normal WBC count is not reassuring.[16] In a French study of 2047 febrile infants seen in 15 pediatric EDs, the area under the curve (AUC) for WBC count was 0.48 compared with 0.61 for ANC.[39] In the PROS study, an abnormal WBC count (<5000/mm^3, >15 000/mm^3) was significant in a multivariate analysis with an adjusted odds ratio of 3.62 (95% CI, 2.13–6.15) and slightly increased the AUC of a non–laboratory-based model from 0.767 to 0.803. The committee does not recommend use of abnormal WBC count for risk stratification.
- ANC: >4000,[18] >5200[60] cells per mm^3. Although arbitrary values of ANC continue to be included in decision models, researchers in 2 studies methodologically derived optimal cutoffs. The subcommittee presents both values (>4000, >5200), reflecting the current state of the evidence.

1. In a prospective study of 1821 febrile infants with 30 cases of IBI younger than 60 days, the PECARN group used recursive partitioning to derive optimal thresholds for detecting IBI. This study found that an ANC of >4090 per mm^3, when combined with an abnormal urinalysis and a procalcitonin of greater than 1.7 ng/mL, detected 29 of 30 cases, 96.7% (95% CI, 83.3%–99.4%) with a specificity of 61.5%.[18] No case of meningitis was missed.
2. The Febrile Young Infant Research Collaborative study did not include procalcitonin but methodologically derived an ANC ≥5185 per mm^3 as part of a scoring system to identify IBIs retrospectively. The sensitivity of its scoring system for 207 cases of IBIs was 98.8% (95% CI, 95.7%–99.9%) but had a specificity of 31.3%; none of the 26 cases of bacterial meningitis was missed.[60]

The step-by-step method proposed by the European Collaborative of 11 EDs[19,20] selected a higher ANC threshold (10 000) for its model and detected 81 of 87 infants with IBIs. No cases of bacterial meningitis were missed; the sensitivity for IBIs was 92% (95% CI, 85.0%–97.2%), lower than the 2 American studies. The only prospective office-based study, using recursive partitioning, did not identify ANC as a predictor for the 63 cases of IBIs.[17]

ANC is helpful but not as accurate as newer IMs.[16] In a subset analysis of 46 infants 8 to 60 days of age with bacterial meningitis, blood ANC ranged from 600 to 24 500, with a median of 4700; 39% had ANCs <4000 and 80% had ANCs <10 000.[17,20] As used in a PECARN analysis, an ANC of <4090 combined with a negative urinalysis result had a sensitivity of 76.6% (95% CI, 0.59%–0.88%); addition of procalcitonin was required to achieve the high sensitivity of its decision rule for IBI.[18] Because of availability, timeliness, and these data, an elevated ANC is a useful IM when combined with other clinical and laboratory predictors.

Although several studies have identified ANC cutoffs for infants at low risk of IBI,[18–20,60] counts <1000 should raise concerns for sepsis in the youngest infants.

- CRP (≥20 mg/L): In studies addressing laboratory markers, CRP has been shown to be more accurate than WBC count or ANC in detecting

KAS 11a: Clinicians may obtain a CSF analysis on infants 22 to 28 days of age even if all of the following criteria are met: (1) urinalysis result is negative or positive; (2) no IM obtained is abnormal; (3) blood and urine cultures have been obtained; and (4) infant is hospitalized. Evidence Quality: B; Moderate Recommendation

Benefits of testing	Early detection of bacterial meningitis. Detection of CSF pleocytosis or elevated protein attributable to HSV infection. Early treatment may decrease neurologic morbidity. Identification of pathogen from CSF to target type and duration of antimicrobial treatment. A normal CSF analysis helps in the decision whether to discharge infants at 24–36 h. Avoids unnecessarily prolonged antimicrobial therapy if CSF was obtained after antimicrobial agents started and diagnosis of meningitis is uncertain. This situation may occur if a blood culture grows a pathogen in 24 h and clinical circumstances suggest an LP is indicated.
Benefits of not testing	Avoids consequences of LP: discomfort or harm. Avoids further medical interventions because of false-positive results from CSF pleocytosis or bacterial contaminants. Avoids unnecessary or prolonged hospitalizations because of false-positive culture results. Avoids cost of procedure and unnecessary hospitalization. Avoids transient respiratory compromise resulting from positioning.
Risk, harm, cost of testing	Discomfort for infant. Potential for transient respiratory compromise during positioning for LP. Traumatic LPs yielding uninterpretable CSFs have been documented to prolong length of stay for hospitalized infants.[132] Unnecessary prolongation of hospitalization from false-positive bacterial culture result. Substantial cost if hospitalizing because of ambiguous CSF or prolonged hospitalization for bacterial contaminant. Parental anxiety.
Risks, harm, cost of not testing	In otherwise low-risk infants, delayed recognition of bacterial meningitis with increased risk of morbidity. Prolonged treatment if delay in obtaining CSF raises concern for partially treated meningitis.
Benefit–harm assessment	Benefit in specified situations.
Shared decision-making	Parents must provide consent for this procedure. An option by the committee to not obtain CSF for analysis is based on a consensus regarding the rate and risks of meningitis and benefit–harm assessment. Parents should be sufficiently informed to participate in this decision.
Key references	17–20, 22, 60, 106, 148

Because the prevalence of bacterial meningitis, along with the prevalence of bacteremia, declines in 22- to 28-d-old infants, the committee's tolerance for this risk resulted in a recommendation that differs from the one for 8- to 21-d-old infants.

bacteremia and meningitis.[39,101,102] As independent predictors of IBIs, the AUC for CRP was documented as 0.77 compared with 0.61 for ANC,[39] with another study producing values of 0.75 and 0.65, respectively.[146] In the absence of procalcitonin and in combination with other clinical predictors, a CRP ≥20 mg/L has identified infants at higher risk.[19,20,101] It generally can be determined in a timely fashion and has recently become available as a point-of-care test.[37]

- Procalcitonin (>0.5 ng/mL): Serum procalcitonin, as an independent predictor of bacterial infections, has better test characteristics than other laboratory markers of inflammation. In a prospective study of 15 French EDs, Milcent et al[39] identified 21 infants 7 to 90 days of age with IBIs. The AUC for procalcitonin, CRP, ANC, and WBC count were documented to be 0.91, 0.77, 0.61, and 0.48, respectively. In this study, a procalcitonin value of 0.3 ng/mL best demarcated low- and high-risk infants and in multivariate analysis was the only independent predictor of IBIs. These findings were replicated in a recent ED study from Spain[146] with 38 infants <60 days of age with IBIs. The AUC for procalcitonin, CRP, and ANC was 0.82, 0.75, and 0.65, respectively. The value of procalcitonin when used in combination with other clinical and laboratory findings is becoming clear.[18–20,38,97–105] Using a procalcitonin level of >0.5 ng/mL, along with other clinical variables, was useful in identifying a low-risk group (0.7%) for IBIs in infants >21 days but an unacceptably low sensitivity of 44% for younger infants.[100] The PECARN study, described above, demonstrated a sensitivity of 96.7% by adding an elevated procalcitonin (1.7 ng/mL) to leukocyturia and ANC >4090 mm^3. Changing the procalcitonin level to 0.5 ng/mL (and the ANC to 4000 mm^3) only minimally decreased rule specificity, so it is advocated by the PECARN investigators as a safer and easier-to-apply cutoff. Procalcitonin is the earliest IM to increase but may still be negative in febrile infants,[18] including those evaluated in the first hours after onset of fever.[146] Although it is currently the best IM available, it should not be used alone for decision-making; 20% of febrile infants with bacterial meningitis had procalcitonin <0.5 ng/mL.[20]

The committee recommends procalcitonin in all age groups. Procalcitonin testing is not yet routinely available in many institutions in the United States. If procalcitonin is unavailable or results are not reported in a timely fashion, the committee recommends using a fever of >38.5°C in combination with other IMs for purposes of risk stratification.

KAS 11a: Clinicians may obtain a CSF analysis on infants 22 to 28 days of age even if all of the following criteria are met:

1. **urinalysis result is negative or positive;**
2. **no IM obtained is abnormal;**

KAS 11b: Clinicians should obtain CSF for analysis (WBC count, protein, glucose, Gram stain) and bacterial culture if any IM obtained Is abnormal. Evidence Quality: C; Moderate Recommendation

Benefits	Early detection of bacterial meningitis. The prevalence of bacterial meningitis in this age group is 0.4% to 0.6%.[24,94] Detection of CSF pleocytosis or elevated protein attributable to HSV infection. Early treatment may lead to decreased neurologic morbidity. Identification of pathogen from CSF to target type and duration of antimicrobial treatment. Avoids unnecessarily prolonged antimicrobial therapy if CSF was obtained after antimicrobial agents started and diagnosis of meningitis is uncertain.
Risks, harm, cost	Discomfort for infant. Potential for transient respiratory compromise during positioning for LP. Traumatic LPs have been documented to prolong length of stay for hospitalized infants. Unnecessary prolongation of hospitalization from false-positive bacterial culture result. Substantial cost if hospitalizing because of ambiguous CSF or prolonged hospitalization for bacterial contaminant. Parental anxiety.
Benefit–harm assessment	Preponderance of benefit for infants with specified risk factors if CSF obtained.
Role of patient preferences	Parents must provide consent for this procedure. KAS 4 extensively discusses rates and consequences of unsuccessful LPs, uninterpretable CSFs, and false-positive bacterial culture rates. If, for whatever reason, a parent is resistant or unwilling to consent to an LP, risk of meningitis, the evidence quality, and benefit/harm assessment should be communicated to the parent to foster informed decision-making. The potential need for a future LP, depending on further clinical information and progress, is an important part of the discussion. These discussions should be documented.
Key references	68–71, 106, 108–139

For detailed discussion, including viral testing, see KAS 4.

3. **blood and urine cultures have been obtained; and**
4. **infant is hospitalized.**

Evidence Quality: B; Moderate Recommendation

There are insufficient data to estimate the probability of meningitis in this age group if only 1 IM is abnormal or if only a urinalysis result is positive. Almost all current decision rules and models rely on a combination of at least 2 IMs and a urinalysis to define risk.

Recent studies from primary care and EDs document LPs in infants <28 days of age being performed in 60% to 82% of evaluations. There is wide regional variation ranging from 10.7% to 31.3% of infants going without an LP.[23,24,148] With recent data, Kaiser Northern California documents 39% of 7- to 28-day-old infants with fever did not undergo LP. Infants evaluated in the ED were 5 times more likely to have an LP than those evaluated in the office.[22] There were no reported cases of delayed recognition of bacterial meningitis in settings in which LPs were not universally performed.

In infants <28 days of age, none of the 21 cases of bacterial meningitis in the PROS, PECARN, and step-by-step studies were missed (sensitivity 100%; CI, 84%–100%). Using a bacterial meningitis prevalence in 22- to 28-day-old infants of 0.39[22] or 0.46[94] or ~1 in 200 to 250 and the lower end of the sensitivity CI (84%) suggests 1250 to 1560 interpretable CSF samples would be required to detect each additional case of bacterial meningitis (number needed to test = 1250–1560). Without procalcitonin, these studies detected 14 of 14 cases of bacterial meningitis (95% CI, 80%–100%), indicating a number needed to test of 1000 to 1250.

Researchers in a few studies have addressed a positive urinalysis result or UTI as a risk factor for meningitis. Data for 22- to 28-day-old infants are limited, as are data for UTI without abnormal IMs. For infants 7 to 30 days of age in the Reducing Variability in the Infant Sepsis Evaluation study of 1281 infants with positive urinalysis results who had an LP performed, 0.8% were treated for bacterial meningitis.[149] This was similar to the 1.0% of the 4644 infants with negative results on the urinalysis. The data also indicated that none of the 98 infants with positive urinalysis results did not have an LP ultimately had meningitis detected. Similarly, in an outpatient study of 100 infants with UTI <30 days of age, researchers found no cases of meningitis.[150] However, in both of these studies, the lower limits of the CI indicates up to 4% could be missed.

KAS 12a: Clinicians should administer parenteral antimicrobial therapy in a hospital if either of the following apply: (1) CSF analysis suggests bacterial meningitis; or (2) urinalysis result is positive. Evidence Quality: A; Strong Recommendation

Benefits	If diagnostic testing indicates the fever is attributable to UTI or bacterial meningitis, the infection would be treated promptly. Anticipated reduction in morbidity or mortality.
Risks, harm, cost	Adverse drug reactions including anaphylaxis (rare). Complications related to intravenous lines including infiltration, infection, nerve compression (in ankle). Potential disruption of evolving microbiome. Development of antimicrobial resistance.
Benefit–harm assessment	Preponderance of benefit.
Key references	3, 57, 145

KAS 12b: Clinicians may administer parenteral antimicrobial therapy in a hospital if all of the following apply: (1) CSF analysis is normal; (2) urinalysis is normal; and (3) any IM obtained is abnormal. Evidence Quality: B; Moderate Recommendation

Benefits	An abnormal IM indicates a risk of bacteremia >5%, a threshold sufficiently high to recommend empirical treatment.
	Anticipated reduction in morbidity and mortality.
Risks, harm, cost	Adverse drug reactions including anaphylaxis (rare).
	Complications related to intravenous lines including infiltration, infection, nerve compression (in ankle).
	Potential disruption of evolving microbiome.
	Development of antimicrobial resistance.
Benefit–harm assessment	Preponderance of benefit.
Key references	3, 57, 145

KAS 11b: Clinicians should obtain csf for analysis (WBC count, protein, glucose, Gram stain) and bacterial culture if any IM obtained is abnormal. Evidence Quality: C; Moderate Recommendation

See note on KAS11a.

INITIAL TREATMENT

The antimicrobial agents in Table 3 are recommended for initial empirical therapy and should be modified following results of cultures and sensitivities.

KAS 12a: Clinicians should administer parenteral antimicrobial therapy in a hospital if either of the following apply:

1. **CSF analysis suggests bacterial meningitis; or**
2. **urinalysis result is positive.**

Evidence Quality: A; Strong Recommendation

KAS 12b: Clinicians may administer parenteral antimicrobial therapy in a hospital if all of the following apply:

1. **CSF analysis is normal;**
2. **urinalysis is normal; and**
3. **any IM obtained is abnormal.**

Evidence Quality: B; Moderate Recommendation

KAS 12c: Clinicians may administer parenteral therapy to hospitalized infants even if all of the following are met:

1. **urinalysis is normal;**
2. **no IM obtained is abnormal; and**
3. **CSF analysis is normal or enterovirus-positive.**

Evidence Quality: B; Weak Recommendation

Recent evidence documents the sensitivity of LE for UTI of 94% (95% CI, 91%–97%),[79] even higher in UTI associated with bacteremia (97.6% and 100% in 2 studies)[80,86]; an NPV of 99% also supports a low likelihood of UTI.[78,85–89] There are insufficient data to estimate precisely the risk of bacterial meningitis with normal CSF analysis, but, based on the scarcity of cases in the literature, the risk appears to be quite low. However, as current prediction rules fail to

TABLE 3 Initial Empirical Antibacterial Therapy for Well-Appearing Febrile Infants 7 to 60 Days Old

Suspected Source of Infection	8–21 d Old	22–28 d Old	29–60 d Old
UTI[a]	Ampicillin IV or IM (150 mg/kg per d divided every 8 h) and either ceftazidime IV or IM (150 mg/kg per d divided every 8 h) or gentamicin IV or IM (4 mg/kg per dose every 24 h)	Ceftriaxone IV or IM (50 mg/kg per dose every 24 h)	Ceftriaxone IV or IM (50 mg/kg/dose every 24 h). Oral medications for infants older than 28 d.[b] Cephalexin 50–100 mg/kg per d in 4 doses or cefixime 8 mg/kg per d in 1 dose
No focus identified[c]	Ampicillin IV or IM (150 mg/kg per d divided every 8 h) and either ceftazidime IV or IM (150 mg/kg per d divided every 8 h) or gentamicin IV or IM (4 mg/kg per dose every 24 h)[d]	Ceftriaxone IV or IM (50 mg/kg per dose every 24 h)	Ceftriaxone IV or IM (50 mg/kg/dose every 24 h)
Bacterial meningitis[e]	Ampicillin IV or IM (300 mg/kg per d divided every 6 h) and ceftazidime IV or IM (150 mg/kg per d divided every 8 h)	Ampicillin IV or IM (300 mg/kg per d divided every 6 h) and ceftazidime IV or IM (150 mg/kg per d divided every 8 h)	Ceftriaxone IV (100 mg/kg per d once daily or divided every 12 h) or Ceftazidime IV (150 mg/kg per d divided every 8 h) and vancomycin[f] IV (60 mg/kg per d divided every 8 h)

Use of a local antibiogram, if available, can guide choices. Note: If a focus of infection such as pneumonia, cellulitis, gastroenteritis, or musculoskeletal infection is identified, different regimens that cover typical microbial pathogens for the site of infection should be administered. IM, intramuscular; IV, intravenous. Adapted from Bradley JS, Nelson JD, Barnett ED, et al, eds. *2019 Nelson's Pediatric Antimicrobial Therapy.* 25th ed. Itasca, IL: American Academy of Pediatrics; 2019; and Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018.

[a] On the basis of urinalysis results.

[b] AAP Subcommittee on Urinary Tract Infection.[73]

[c] For example, possible bacteremia. For 22 to 28 day old infants, providers may decide that observation without initiation of therapy is appropriate after risk versus benefit discussion with the infant's parents or caregivers.

[d] Gentamicin may provide clinical benefit because of synergy with ampicillin against GBS and enterococcal species.

[e] On the basis of CSF analysis results. Some experts will add gentamicin or another aminoglycoside to this regimen, particularly if the CSF Gram stain reveals Gram-negative organisms.

[f] Vancomycin is part of empirical therapy because of the possibility of resistant *S pneumoniae*. It should be stopped if an organism other than *S pneumoniae* is identified, even if susceptibilities are still pending.

KAS 12c: Clinicians may administer parenteral therapy to hospitalized infants even if all of the following are met: (1) urinalysis is normal; (2) no IM obtained is abnormal; and (3) CSF analysis is normal or enterovirus-positive. Evidence Quality: B; Weak Recommendation

Benefits	Of treating: If etiology of fever is bacteremia, the infection would be treated promptly. Anticipated reduction in morbidity and mortality. Of not treating: No adverse drug reactions. No complication of intramuscular administration. No disruption of infant's evolving microbiome. Delayed development of antimicrobial resistance.
Risks, harm, cost	Of treating: Adverse drug reactions including anaphylaxis (rare). Complication of intramuscular administration. Potential disruption of evolving microbiome. Development of antimicrobial resistance. Of not treating: If etiology of fever is bacteremia not suspected by risk stratification, the infection could potentially progress. Potential increase in morbidity or mortality.
Benefit–harm assessment	Balanced.
Key references	3, 57, 145

detect about 3% to 8% of bacteremia cases, antimicrobial agents may be administered.[18,20]

KAS 12d: Clinicians should use parenteral antimicrobial therapy for infants who will be managed at home even if all of the following are met:

1. **urinalysis is normal;**
2. **no IM obtained is abnormal; and**
3. **CSF analysis is normal.**

Evidence Quality: C; Moderate Recommendation

If all IMs are normal and urinalysis and CSF analysis do not suggest infection, the risk of bacteremia is between 1% and 2% (number needed to treat 50–100).

KAS 12d: Clinicians should use parenteral antimicrobial therapy for infants who will be managed at home even if all of the following are met: (1) urinalysis is normal; (2) no IM obtained is abnormal; and (3) CSF analysis is normal. Evidence Quality: C; Moderate Recommendation

Benefits	If etiology of fever is bacteremia, the infection would be treated promptly without the delay involved in returning to hospital. Anticipated reduction in morbidity and mortality.
Risks, harm, cost	Adverse drug reactions including anaphylaxis (rare). Complication of intramuscular administration. Potential disruption of evolving microbiome. Development of antimicrobial resistance.
Benefit–harm assessment	Preponderance of benefit.
Key references	3, 57, 145

KAS 13a: Clinicians may manage infants at home if all of the following criteria are met:

1. **urinalysis is normal;**
2. **no IM obtained is abnormal;**
3. **CSF analysis is normal or enterovirus-positive;**
4. **verbal teaching and written instructions have been provided for monitoring throughout the period of time at home for the following:**
   - **change in general appearance, particularly a dusky color, or respiratory or other distress;**
   - **behavior change, including lethargy, irritability, inconsolable crying, difficulty in consoling/comforting, or other evidence of distress;**
   - **difficulty feeding;**
   - **vomiting; and**
   - **decreased urine output;**
5. **follow-up plans for reevaluation in 24 hours have been developed and are in place; and**
6. **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.**

Evidence Quality: B; Moderate Recommendation

Value judgments: The committee values careful infant monitoring provided by hospital staff skilled in the care of neonates and young infants. In some situations, infants may not be hospitalized because of lack of access to a local hospital unit able to care for young infants (in which case referral to a regional hospital is an acceptable alternative) or other circumstances. In primary care settings, in which close follow-up is possible, more than 30% of low-risk infants are managed at home after initial evaluation.[17,22] For infants seen in EDs, 15% to 30% are not hospitalized.[23,24] In these studies, the subsequent admission rate is 1% to 2%; delays in treating bacterial infections have been rare. Several recent studies suggest otherwise low-risk infants in the absence of CSF data may be of sufficiently low risk to safely be managed at home after initial evaluation.[18,20]

For infants discharged from the hospital after initial evaluation, phone or other telecommunication contact should be attempted and documented at appropriate intervals after returning home. Infants should be scheduled for repeat clinical evaluation within the next 24 hours or sooner, if deemed appropriate. If at 24 hours, the parents report no clinical worsening and all culture results are negative, a phone

KAS 13a: Clinicians may manage infants at home if all of the following criteria are met: (1) urinalysis is normal; (2) no IM obtained is abnormal; (3) CSF analysis is normal or enterovirus-positive; (4) verbal teaching and written instructions have been provided for monitoring throughout the period of time at home; (5) follow-up plans for reevaluation in 24 h have been developed and are in place; and (6) 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. Evidence Quality: B; Moderate Recommendation

Benefits	Potential reduction of family disruption and stress. Improved circumstances for breastfeeding. Decreased risk of iatrogenic consequences of hospitalization. Eliminates risk of hospital-acquired infection. Less costly.
Risks, harm, cost	Delayed response if there is a clinical change potentially indicating infection progression. Potential increase in parental anxiety and fatigue. Dependent on parental ability to judge clinical change in a newborn infant.
Benefit–harm assessment	Preponderance of benefit in low-risk infants if discharge criteria are met.
Shared decision-making	For low-risk infants, the decision whether to hospitalize or not should be made after physicians provide estimates of the risks of underlying IBIs and benefits of home versus hospital monitoring. Parents and physicians have different values for clinical outcomes in young febrile infants. It has been documented that parents place greater value on short-term benefits such as avoiding pain, discomfort, and errors in diagnostic testing while physicians gave greater wt to avoiding short- and long-term morbidity.[66,67] These and other inherent value differences should be considered when engaging in discussions. Also, individual parents and physicians have different tolerances for risk.[66–71]
Key references	17, 22–24

The benefit/harm ratio of hospitalizing depends, in large part, on reducing the risk of sending home an infant with undiagnosed, untreated meningitis. In KAS 11b, the committee estimated the risk of meningitis going undetected and can estimate that 1200 to 1500 febrile infants would require hospitalization to avoid 1 infant going home with undetected bacterial meningitis. The benefit/harm assessment is also dependent on the quality of observation and monitoring in each hospital compared with parents' abilities to recognize any worsening of illness and return promptly.

conversation may be sufficient for follow-up. Transportation difficulty is a contributor to health inequity. Given the importance of the ability to return for changes in clinical status and further evaluations we recommend institutions consider travel vouchers (taxi or ride-share) for families with transportation insecurity. Telemedicine is increasingly being used for follow-up visits and may be appropriate in some situations.

If the reevaluation will be performed at another location or by a different clinical evaluator, it is recommended that the site for medical reevaluation be arranged in advance and clinician-to-clinician communication be direct. Clear written and documented instructions should be given to parents as to the time and place of the return visit.

KAS 13b: Clinicians should hospitalize infants in a facility with nurses and staff experienced in the care of neonates/young infants when CSF is not obtained or is uninterpretable. Evidence Quality: B; Weak Recommendation

FURTHER MANAGEMENT AND MONITORING

KAS 14a: Clinicians should discontinue antimicrobial agents and discharge hospitalized infants after 24 to 36 hours of negative culture results if the following are met:

1. **the infant is clinically well or improving (eg, fever, feeding);**
2. **there are no other reasons for hospitalization; and**
3. **there is no other infection requiring treatment (eg, otitis media).**

Evidence Quality: B; Strong Recommendation

In the most recent large studies, bacterial pathogens were not detected by 24 h in 15% to 18% and longer than 36 h in 5% to 7%; for CSF, the respective times were 11% to 18% and 6% to 15%.[138,139] Growth by 24 h occurred in a lower proportion of well-appearing infants with bacteremia (85%) compared with ill-appearing infants (93%).[138]

KAS 14b: Clinicians should discontinue antimicrobial agents on infants managed at home when all of the following criteria are met:

1. **infant is clinically well or improving (eg, fever, feeding) at time of reassessment;**
2. **all cultures are negative at 24 to 36 hours; and**
3. **there is no other infection requiring treatment (eg, otitis media).**

Evidence Quality: B; Strong Recommendation

KAS 14c: Clinicians should treat infants' positive bacterial pathogens in urine, blood, or CSF with targeted antimicrobial therapy for the duration of time consistent with the nature of the disease, responsible organism, and response of the infant to treatment. Evidence Quality: A; Strong Recommendation

WELL-APPEARING 29- TO 60-DAY-OLD-INFANTS

Diagnostic Evaluation

The following recommendations and options are for febrile (temperature >38.0°C), well-appearing, term infants 29 to 60 days of age without risk factors identified in the exclusion criteria.

KAS 13b: Clinicians should hospitalize infants in a facility with nurses and staff experienced in the care of neonates/young infants when CSF is not obtained or is uninterpretable. Evidence Quality: B; Weak Recommendation

Benefits	Opportunity for observation by skilled, experienced staff and ability to administer treatment promptly if condition worsens.
Risks, harm, cost	Hospitalization increases risk of hospital-acquired infections. Increased risk of iatrogenic events related to intravenous catheters. Parental anxiety about infant's condition and financial strain. Stress to mothers because of breastfeeding challenges and separation from other children. Substantial cost.
Benefit–harm assessment	Balanced.
Shared decision-making	In 13a, criteria for an infant to be managed at home include normal CSF analysis. For clinicians and parents, having jointly decided on an LP, a result with inadequate or confusing CSF analysis presents a dilemma. Risks should be reviewed, and parents should understand the assessment of benefit- harm. Likelihood of missing meningitis with a variety of decision rules and models is discussed in KAS 10. For uninterpretable CSF, an ME panel may assist decision-making.
Key references	3, 57, 151

KAS 15: Clinicians should obtain urine specimen by bag, spontaneous void, or stimulated void for urinalysis and, if urinalysis result is positive, obtain a catheterization or SPA specimen for culture, or obtain urine specimen by catheterization or SPA of bladder for urinalysis and, if result is positive, for culture. Evidence Quality A; Strong Recommendation

Circumcised boys have a likelihood of UTI <1% and may be exempted from this recommendation.

Although the sensitivity of LE is not 100%, the rate of positive urine culture results without an abnormal urinalysis is roughly the same as the rate of asymptomatic bacteriuria and contamination. Moreover, renal scarring appears to be mediated by host WBCs rather than the presence of bacteria.

In one high-volume ED, limiting catheterizations to children with positive urine screen results from bag specimens reduced catheterization rates by more than half (63%–<30%) without increasing length of time in the facility or missing any UTIs.[85] Use of bladder-stimulation techniques[84] is more time-efficient than urine bag collection.[83] In newborn infants, bladder and lumbar stimulation was highly successful in facilitating midstream urine collection in a median time of 45 seconds.[90] Specimens obtained by methods other than catheterization or SPA are not suitable for culture because of a high contamination rate.[77,78]

KAS 14a: Clinicians should discontinue antimicrobial agents and discharge hospitalized infants after 24 to 36 hours of negative culture results if the following are met: (1) the infant is clinically well or improving (eg, fever, feeding); (2) there are no other reasons for hospitalization; and (3) there is no other infection requiring treatment (eg, otitis media). Evidence Quality: B; Strong Recommendation

Benefits	Minimizes exposure to hospital-acquired infections and iatrogenic exposures. Limits family disruption. Reduces cost of illness episode.
Risks, harm, cost	Inadequate duration of therapy with antimicrobial for bacterial pathogen not identified before discontinuation at 24 h (5%–18%) or 36 h (<5%).
Benefit–harm assessment	Preponderance of benefit.
Key references	57, 138–144

KAS 16: Clinicians should obtain a blood culture. Evidence Quality: B; Moderate Recommendation

The prevalence of bacteremia is lower than in the younger groups of infants but still high enough to warrant a blood culture (see Fig 4).

KAS 17: Clinicians should assess IMs. Evidence Quality: B; Moderate Recommendation

For detailed discussion of IMs, see KAS 10.

KAS 18a: Clinicians may obtain CSF for analysis (WBC count, differential, protein, glucose, Gram stain), culture for bacteria, and test for enterovirus when CSF pleocytosis is detected or during enterovirus season if any IM obtained is abnormal. Evidence Quality: C; Weak Recommendation

There is substantial evidence IMs are predictive of IBI including bacterial meningitis.[10–14,16,18–20] For this age group, the number of meningitis cases in published studies is still relatively small, 64 cases in 25 917 febrile infants (0.25%). Data are unavailable comparing prevalence in IM-positive versus IM-negative infants, but decision rules and models that include IMs have sensitivities greater than 90%. In KAS 10, the committee provided data indicating that individual IMs are seldom sensitive or specific for detecting bacteremia or meningitis. However, individual values that are exceedingly high or low or finding several abnormal IMs should be considered in decision-making, because they, in all likelihood, increase the risk of bacterial meningitis.

KAS 14b: Clinicians should discontinue antimicrobial agents on infants managed at home when all of the following criteria are met: (1) infant is clinically well or improving (eg, fever, feeding) at time of reassessment; (2) all cultures are negative at 24 to 36 hours; and (3) there is no other infection requiring treatment (eg, otitis media). Evidence Quality: B; Strong Recommendation

Benefits	Minimizes risk of adverse treatment consequences. Reduces impact on microbiome. Contributes to antimicrobial stewardship.
Risks, harm, cost	Inadequate duration of therapy with antimicrobial for bacterial pathogen not identified before discontinuation at 24 h (5%–18%) or 36 h (<5%).
Benefit–harm assessment	Preponderance of benefit.
Key references	138–144

KAS 18b: Clinicians need not obtain CSF for analysis and culture if all IMs obtained are normal. Evidence Quality: B; Moderate Recommendation

The committee supports not performing an LP in well-appearing infants meeting the specified criteria. For an estimated prevalence of meningitis in 29- to 60-d-old infants of 0.25% and using a prediction rule or model with a sensitivity of 90%, the chance of missing a case of meningitis would be 0.025%. Therefore, 4000 successful LPs would be required to avoid a delay in the detection of 1 case of bacterial meningitis.

If no IM is abnormal, the committee does not include a positive urinalysis result as an indicator for performing an LP.

INITIAL TREATMENT

The antimicrobial agents in Table 3 are recommended for initial empirical therapy and should be modified following results of cultures and sensitivities.

KAS 19a: Clinicians should use parenteral antimicrobial therapy if CSF analysis suggests bacterial meningitis. Evidence Quality: A; Strong Recommendation

If CSF is not available or is uninterpretable, clinicians should use parenteral antimicrobial agents.

KAS 19b: Clinicians may use parenteral antimicrobial therapy if both of the following apply:

1. **CSF analysis (if CSF obtained) is normal; and**
2. **any IM obtained is abnormal.**

Evidence Quality: B; Moderate Recommendation

If CSF is positive for enterovirus, clinicians may discontinue (or withhold) antimicrobial agents as long as there are no other factors suggesting a bacterial infection, including abnormal IMs.

KAS 14c: Clinicians should treat infants' positive bacterial pathogens in urine, blood, or CSF with targeted antimicrobial therapy for the duration of time consistent with the nature of the disease, responsible organism, and response of the infant to treatment. Evidence Quality: A; Strong Recommendation

Benefits	Inhibits further growth of bacterial pathogen. Cures infection. Reduces likelihood of morbidity. Contributes to antimicrobial stewardship.
Risks, harm, cost	Adverse reaction to antimicrobial. Interferes with infant's evolving microbiome. Accelerates emergence of antimicrobial resistance.
Benefit–harm assessment	Preponderance of benefit.
Key references	145

KAS 19c: Clinicians should initiate oral antimicrobial therapy if all of the following apply:

1. **CSF analysis (if CSF obtained) is normal;**
2. **urinalysis result is positive; and**
3. **no IM obtained is abnormal.**

Evidence Quality: B; Strong Recommendation

KAS 19d: Clinicians need not use antimicrobial therapy while awaiting bacterial culture results if all of the following are met:

1. **CSF analysis, if CSF obtained, is normal or enterovirus-positive;**
2. **urinalysis is negative; and**
3. **no IM obtained is abnormal.**

Evidence Quality: B; Moderate Recommendation

The risk for well-appearing infants with these negative findings having bacteremia is 0.1% for infants 29 to 60 days of age,[18] with a CI upper limit that indicates the number needed to test is >300. Recent evidence documents the sensitivity of LE for UTI of 94% (95% CI, 91%–97%),[80] even higher in UTI associated with bacteremia (97.6% and 100%) in 2 studies[80,86]; an NPV of 99% also supports a low likelihood of UTI.[38–40] There are insufficient data to estimate precisely the risk of bacterial meningitis with normal CSF analysis, but, based on the scarcity of cases in the literature, the risk appears to be quite low.

Value Judgments: There were different thresholds, within the committee, for treating with antimicrobial agents. The potential benefits are highlighted above. The overall sense of the committee was to administer antimicrobial agents if the number needed to test for bacteremia is 100 or less: that is, willing to treat as many as 100 infants with parenteral antimicrobial agents to avoid delaying treatment in 1 infant with

KAS 15: Clinicians should obtain urine specimen by bag, spontaneous void, or stimulated void for urinalysis and, if urinalysis result is positive, obtain a catheterization or SPA specimen for culture, or obtain urine specimen by catheterization or SPA of bladder for urinalysis and, if result is positive, for culture. Evidence Quality A; Strong Recommendation

Benefits	Identification of UTIs. A positive urinalysis result prompts initiation of empirical antimicrobial therapy. A positive urine culture result for pathogenic bacteria directs appropriate antimicrobial treatment. A negative urinalysis result signifies a low likelihood of a UTI and obviates catheterization or SPA (if not already performed).
Risks, harm, cost	Falsely positive culture result (contamination) or misdiagnosis of asymptomatic bacteriuria leading to unnecessary and potentially harmful treatment and inaccurate documentation of a first UTI (which may prompt unnecessary imaging should a UTI occur subsequently). Discomfort of catheterization or SPA. Parent anxiety.
Benefit–harm assessment	Preponderance of benefit.
Shared decision-making	Because nearly 90% of febrile infants will not have UTIs, obtaining a screening specimen through noninvasive methods is appropriate. Voided methods can be offered with explanations of a potential time delay and need for a second urine sample obtained by catheterization and/or SPA if initial urine screen result is positive. Parents opposed to catheterization should be offered a choice of SPA and informed about the higher rate of ambiguous or false-positive culture results obtained from bagged or voided specimens.[77] A false-positive urine culture result can potentially prolong antimicrobial administration.
Key references	73, 77–93

KAS 16: Clinicians should obtain a blood culture. Evidence Quality: B; Moderate Recommendation

Benefits	Identification of bacteremia: 1.1%–2.2% of all febrile infants in this age group[17,22,24,61,94] and 5%–10% in infants with UTI.[17,26,91–93,152,153] Identification of organism (and sensitivities) for directed antimicrobial treatment. Early detection and treatment may prevent progression of infection.
Risks, harm, cost	False-positive results: Most positive blood cultures in febrile infants are attributable to contaminants[25,27,28,30] potentially leading to unnecessary use of antimicrobial agents, further or repeat testing, and prolonged hospitalization. Discomfort of venipuncture. Costs can be substantial depending on further testing, treatment, and hospitalization after a false-positive culture result.
Benefit–harm assessment	Preponderance of benefit.
Role of patient preferences	Parents should understand that testing is based on the high likelihood of bacteremia, especially in infants with positive urinalysis result. Parents can be informed of potential challenges that may be encountered in distinguishing pathogens from contaminants as part of explaining the evaluation process.
Key references	22, 24, 30, 61

bacteremia. The committee recognizes that parents and practitioners have different levels of risk aversion and thresholds for treatment that should be incorporated into decision-making.

KAS 20a: Clinicians should hospitalize infants in a unit with nurses and staff experienced in the care of 29- to 60-day-old infants if CSF analysis, if CSF obtained, is abnormal. Evidence Quality: A; Strong Recommendation

KAS 20b: Clinicians may hospitalize infants in a unit with nurses and staff experienced in the care of 29- to 60-day-old-infants if any IM obtained is abnormal. Evidence Quality: B; Moderate Recommendation

In a PECARN substudy of 29- to 60-d-old infants, an ANC > 4000 per mm^3 and/or procalcitonin >0.5 ng/mL had a bacteremia prevalence of 3.2%; the prevalence if these IMs were negative was 0.2%.[18]

KAS 20c: Clinicians should manage patients at home if all of the following criteria are met:

1. **CSF analysis, if CSF obtained, is normal;**
2. **urinalysis is negative;**
3. **all IMs obtained are normal;**
4. **appropriate parental education has been provided;**
5. **follow-up plans for reevaluation in 24 hours have been developed and are in place; and**
6. **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.**

Evidence Quality: B; Moderate Recommendation

Value judgments: The low risk of bacteremia and meningitis in infants without positive IMs can potentially reduce hospitalizations without compromising infant safety.

KAS 17: Clinicians should assess IMs. Evidence Quality: B; Moderate Recommendation

Benefits	For infants with negative urinalysis and/or pending urine and/or blood cultures, IMs may influence the decision whether to perform an LP, initiate antimicrobial agents, or hospitalize. For an infant with a negative urinalysis and pending blood culture, the absence of abnormal IMs may contribute to the decision of whether to send the infant home without antimicrobial agents.
Risks, harm, cost	False-negative results, underestimating risk of bacteremia and bacterial meningitis.[23,39] False-positive results, overestimating the risk of bacteremia or bacterial meningitis.
Benefit–harm assessment	Preponderance of benefit.
Key references	13–16, 18–20, 37–39, 60, 97–105, 146

KAS 20d: Clinicians may manage infants without antimicrobial treatment at home without having obtained interpretable CSF if all of the following are met:

1. **urinalysis is negative;**
2. **all IMs obtained are normal; and**
3. **parents can return promptly if there is a change in infant condition and agree to follow-up in 24 to 36 hours. Infants monitored at home should be reassessed in the following 24 hours.**

Evidence Quality: B; Moderate Recommendation

Value judgments: The low risk of bacteremia and meningitis in infants without positive IMs can potentially reduce hospitalizations without compromising infant safety.

KAS 18a: Clinicians may obtain CSF for analysis (WBC count, differential, protein, glucose, Gram stain), culture for bacteria, and test for enterovirus when CSF pleocytosis is detected or during enterovirus season if any IM obtained is abnormal. Evidence Quality: C; Weak Recommendation

Benefits	The prevalence of meningitis in this age group is 0.12–0.32.[17,22,24,61,94] Early detection of meningitis. Early treatment may lead to decreased neurologic morbidity. Identification of pathogen from CSF to target type and duration of antimicrobial treatment. Avoids unnecessarily prolonged antimicrobial therapy if CSF was obtained after antimicrobial agents started and diagnosis of meningitis is uncertain.
Risks, harm, cost	Discomfort for infant. Potential for transient respiratory compromise during positioning for LP. Traumatic LPs have been documented to prolong length of stay for hospitalized infants. Unnecessary prolongation of hospitalization from false-positive bacterial culture result. Substantial cost if hospitalizing because of ambiguous CSF or prolonged hospitalization for bacterial contaminant. Parental anxiety.
Benefit–harm assessment	Preponderance of benefit if CSF obtained.
Shared decision-making	Because parents must consent for this procedure, shared decision-making is required and their risk tolerances a consideration. KAS 4 extensively discusses rates and consequences of unsuccessful LPs, uninterpretable CSF analysis, and false-positive bacterial culture rates. If, for whatever reason, a parent is resistant or unwilling to consent to an LP, risk of meningitis, the evidence quality, benefit/harm assessment, and value judgments should be communicated to the parent to foster informed decision-making. The potential need for a future LP, depending on further clinical information and progress, is an important part of the discussion. These discussions should be documented.
Key references	17, 22, 24, 106, 132, 148

FURTHER MANAGEMENT AND MONITORING

KAS 21a: Clinicians should discontinue antimicrobial agents when all of the following are met:

1. **all bacterial cultures are negative at 24 to 36 hours;**
2. **infant is clinically well or improving (eg, fever, feeding); and**
3. **there is no other infection requiring treatment (eg, otitis media).**

Evidence Quality: B; Strong Recommendation

KAS 21b: Clinicians should discharge hospitalized patients with positive urine culture results (UTI) if all of the following are met:

1. **blood culture is negative;**
2. **CSF culture, if CSF obtained, is negative;**
3. **infant is clinically well or improving (eg, fever, feeding); and**
4. **there are no other reasons for hospitalization.**

Evidence Quality: B; Strong Recommendation

KAS 21c: Clinicians should discontinue parenteral antibiotics (if started) and begin or continue oral antimicrobial for infants with UTIs managed at home when all of the following are met:

1. **urine culture result is positive;**
2. **all other bacterial culture results are negative at 24 to 36 hours; and**
3. **infant is clinically well or improving (eg, fever, feeding).**

Evidence Quality: B; Strong Recommendation

KAS 18b: Clinicians need not obtain CSF for analysis and culture if all IMs obtained are normal. Evidence Quality: B; Moderate Recommendation

Benefits	Avoids unnecessary costs and discomfort of testing in low-risk infant.
Risks, harm, cost	Potential missed opportunity for early detection of developing meningitis.
Benefit–harm assessment	Preponderance of benefit.
Role of parent preferences	Parents should understand the benefit/harm assessment underlying this decision.
Key references	17, 22, 24, 106, 148

KAS 21d: Clinicians should treat infants' positive bacterial pathogens in urine, blood, or CSF with targeted antimicrobial therapy for the duration of time consistent with the nature of the disease, responsible organism, and response of the infant to treatment. Evidence Quality: A; Strong Recommendation

FUTURE RESEARCH

Many of the unanswered questions faced in the committee's review emanated from the challenges of conducting prospective research in clinical settings with a relatively uncommon symptom. Fever in this age group has an incidence rate of 14 per 1000 term, previously healthy births per year.[22] Although >10% of febrile infants will have UTIs, the likelihood of more IBIs is much less, with bacteremia detected in <2% of febrile infants and bacterial meningitis in <0.5%. Negative outcomes, such as permanent renal damage and organ damage or death, from sepsis are rare. Permanent neurologic sequelae from bacterial meningitis occur in variable rates depending on the severity of the infection, onset of treatment, and organism. Therefore, although use of administrative databases has recently provided important information, large, prospective studies will be required to answer a number of the following questions to further refine clinical recommendations for preventing negative outcomes.

KAS 19a: Clinicians should use parenteral antimicrobial therapy if CSF analysis suggests bacterial meningitis. Evidence Quality: A; Strong Recommendation

Benefits	Anticipated reduction in morbidity and mortality from bacterial meningitis.
Risks, harm, cost	Adverse drug reactions including anaphylaxis (rare). Complications related to intravenous lines including infiltration, infection, nerve compression (in ankle). Potential disruption of evolving microbiome. Development of antimicrobial resistance.
Benefit–harm assessment	Preponderance of benefit.
Key references	107, 145

KAS 19b: Clinicians may use parenteral antimicrobial therapy if both of the following apply: (1) CSF analysis (if CSF obtained) is normal; and (2) any IM obtained is abnormal. Evidence Quality: B; Moderate Recommendation

Benefits	Anticipated reduction in morbidity and mortality if infant has bacteremia. The risk of bacteremia is 1.1%–2.1% of all febrile infants in this age group.[17,22,24,94] Identification of organism (and sensitivities) for directed antimicrobial treatment. Early detection and treatment may prevent progression of infection.
Risks, harm, cost	Adverse drug reactions including anaphylaxis (rare). Complications related to intravenous lines including infiltration, infection, nerve compression (in ankle). Potential disruption of evolving microbiome. Development of antimicrobial resistance.
Benefit–harm assessment	Preponderance of benefit.
Key references	17, 22, 145

All of the following pertain to well appearing febrile infants 8 to 60 days of age.

1. Because analyzing data for SBI has obscured understanding of optimal approaches to detect and manage individual infections, the term "SBI" should be retired and the incidence of the following infections determined separately: a. bacterial meningitis; b. bacteremia; and c. UTI.
2. The incidence of each individual infection can then be used to identify the most appropriate age groupings expressed in days rather than the arbitrary ones currently in use (weeks, months). The age groupings used in this guideline are primarily based on data gathered by week of age, as set a priori; although expressed here in days corresponding to those weeks, age groupings in the future should be derived from day-by-day data, which may generate different age groupings from the ones used here.
3. What is the morbidity and mortality of each infection for each age group?
4. What is the current epidemiology of each infection for each age group?
5. What is the best predictive rule for each infection?
6. What is the optimal initial choice and route of antimicrobial agents?
7. What is the optimal duration of therapy?
8. What are the predictors for bacteremia and for bacterial meningitis in a patient with a positive urinalysis result?
9. When does bacteremia matter in an infant with a UTI? Should

KAS 19c: Clinicians should initiate oral antimicrobial therapy if all of the following apply: (1) CSF analysis (if CSF obtained) is normal; (2) urinalysis result is positive; and (3) no IM obtained is abnormal. Evidence Quality: B; Strong Recommendation

Benefits	Inhibits further growth of bacterial pathogen. Reduces likelihood of morbidity.
Risks, harm, cost	Antimicrobial reactions and altering microbiome.
Benefit–harm assessment	Preponderance of benefit.
Key references	155

bacteremia affect treatment duration?

10. In what ways do patients referred to EDs differ from patients initially seeking care in EDs and from patients seen in community practices, and should management differ accordingly?
11. What will be the impact of newer biomarkers and of genomic and other "omic" testing?
12. How should results of multiplex viral testing be incorporated into prediction models for IBI?
13. What is the best way to individualize care? Most guidelines seek to maximize care for the vast majority of patients while allowing for individualized judgments to incorporate certain circumstances. However, most guidelines sort on a small number of variables while most patients present with a vast number of relevant factors. Collaborative efforts that generate consistently acquired patient characteristics have an opportunity, using newer statistical techniques, to match a patient with a presenting symptom to others who most closely resemble the patient's own background and clinical features. In this way, it would be possible to create an individualized guideline for each patient or "one patient, one guideline."
14. Research to individualize care must include patient factors, including better understanding of the role of patient preferences, decision-making, perceptions of risk and vulnerability, satisfaction, and understanding of care.
15. What is the most effective way to provide ongoing monitoring and follow-up? The role of telehealth and differing systems of care approaches should be explored.
16. For low-risk infants, what impact will this guideline have on reducing the use of antimicrobial agents, decreasing invasive diagnostic testing, decreasing hospitalizations, and shortening hospital lengths of stay?
17. What is the impact of individual social determinants of health on risk of IBI, diagnostic testing, management, morbidity and

KAS 19d: Clinicians need not use antimicrobial therapy while awaiting bacterial culture results if all of the following are met: (1) CSF analysis, if CSF obtained, is normal or enterovirus-positive; (2) urinalysis is negative; and (3) no IM obtained is abnormal. Evidence Quality: B; Moderate Recommendation

Benefits	Reduced risk of adverse reaction to antimicrobial agents/ anaphylaxis. Minimize disruption in developing microbiome. Small cost savings.
Risks, harm, cost	Delay in treatment of UTI, bacteremia, or bacterial meningitis with potential disease progression and increased morbidity.
Benefit–harm assessment	This is a benefit for infants receiving close and active observation, as previously discussed.
Key references	17–20, 36

KAS 20a: Clinicians should hospitalize infants in a unit with nurses and staff experienced in the care of 29- to 60-day-old infants if CSF analysis, if CSF obtained, is abnormal. Evidence Quality: A; Strong Recommendation

Benefits	An infant with a positive CSF analysis requires hospitalization for treatment and monitoring. Having the infant immediately available facilitates antimicrobial changes when culture and sensitivity results are reported, particularly if the organism is not sensitive to antimicrobial agents being administered.
Risks, harm, cost	Hospitalization increases risk of hospital-acquired infections. Increased risk of iatrogenic events related to intravenous catheters. Parental anxiety about infant's condition and financial strain. Stress to mothers because of breastfeeding challenges and separation from other children. Substantial cost.
Benefit–harm assessment	Preponderance of benefit.
Key references	57

KAS 20b: Clinicians may hospitalize infants in a unit with nurses and staff experienced in the care of 29- to 60-day-old-infants if any IM obtained is abnormal. Evidence Quality: B; Moderate Recommendation

Benefits	The risk of bacteremia is increased if an IM is abnormal.
Risks, harm, cost	Hospitalization increases risk of hospital-acquired infections. Increased risk of iatrogenic events related to intravenous catheters. Parental anxiety about infant's condition and financial strain. Stress to mothers because of breastfeeding challenges and separation from other children. Substantial cost.
Shared decision-making	For low-risk infants, the decision whether to hospitalize or not should be made after physicians provide estimates of the risks of underlying IBIs and benefits of home versus hospital monitoring. Parents and physicians have different values for clinical outcomes in young febrile infants.[67–73] These inherent value differences should be considered when engaging in discussions. Also, individual parents and physicians have different tolerances for risk.
Benefit–harm assessment	Preponderance of benefit.
Key references	4, 17, 22, 24, 58

KAS 20c: Clinicians should manage patients at home if all of the following criteria are met: (1) CSF analysis, if CSF obtained, is normal; (2) urinalysis is negative; (3) all IMs obtained are normal; (4) appropriate parental education has been provided; (5) follow-up plans for reevaluation in 24 hours have been developed and are in place; and (6) 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. Evidence Quality: B; Moderate Recommendation

Benefits	Active monitoring for infants at increased risk of bacteremia.
Risks, harm, cost	Delay in recognizing changing clinical course warranting further evaluation. Potential increase in parental anxiety.
Benefit–harm assessment	Preponderance of benefit. This is an important consideration for infants when close and active observation is available at home.
Shared decision-making	For low-risk infants, the decision whether to hospitalize or not should be made after physicians provide estimates of the risks of underlying IBIs and benefits of home versus hospital monitoring. Parents and physicians have different values for clinical outcomes in young febrile infants.
Key references	4, 10, 14, 15, 17–21, 36

KAS 20d: Clinicians may manage infants without antimicrobial treatment at home without having obtained interpretable CSF if all of the following are met: (1) urinalysis is negative; (2) all IMs obtained are normal; and (3) parents can return promptly if there is a change in infant condition and agree to follow-up in 24 to 36 hours. Infants monitored at home should be reassessed in the following 24 hours. Evidence Quality: B; Moderate Recommendation

Benefits	Minimize disruption to family attachment and maternal breastfeeding. Substantial cost savings. Reduced risk of iatrogenic events and hospital borne infections.
Risks, harm, cost	Delay in recognizing changing clinical course warranting further evaluation. Potential increase in parental anxiety.
Benefit–harm assessment	Preponderance of benefit.
Key references	4, 10, 14, 15, 17–20, 36

KAS 21a: Clinicians should discontinue antimicrobial agents when all of the following are met: (1) all bacterial cultures are negative at 24 to 36 hours; (2) infant is clinically well or improving (eg, fever, feeding); and (3) there is no other infection requiring treatment (eg, otitis media). Evidence Quality: B; Strong Recommendation

Benefits	Limits costs, disruption to microbiome, adverse reaction.
Risks, harm, cost	Potential inadequate treatment of bacteremia if pathogen grows after 24 h: 5%–15%; after 36 h: $<$5%.
Benefit–harm assessment	Preponderance of benefit.
Key references	57, 92, 138–144

KAS 21b: Clinicians should discharge hospitalized patients with positive urine culture results (UTI) if all of the following are met: (1) blood culture is negative; (2) CSF culture, if CSF obtained, is negative; (3) infant is clinically well or improving (eg, fever, feeding); and (4) there are no other reasons for hospitalization. Evidence Quality: B; Strong Recommendation

Benefits	Limits costs, exposure to hospital-acquired infections, family disruption.
Risks, harm, cost	Potential clinical deterioration if pathogen grows from blood after discharge.
Benefit–harm assessment	Preponderance of benefit.
Key references	153–155

KAS 21c: Clinicians should discontinue parenteral antibiotics (if started) and begin or continue oral antimicrobial for infants with UTIs managed at home when all of the following are met: (1) urine culture result is positive; (2) all other bacterial culture results are negative at 24 to 36 hours; and (3) infant is clinically well or improving (eg, fever, feeding). Evidence Quality: B; Strong Recommendation

Benefits	Ensures adequacy of treatment. Reduced discomfort from parenteral administration. Reduced risk of intravenous infiltration. Reduced disruption to family.
Risks, harm, cost	Potential inadequate treatment of bacteremia if pathogen grows after 24 h: 5%–15%; after 36 h: <5%.
Benefit/harm assessment	Preponderance of benefit.
Key references	138–144, 155

KAS 21d: Clinicians should treat infants' positive bacterial pathogens in urine, blood, or CSF with targeted antimicrobial therapy for the duration of time consistent with the nature of the disease, responsible organism, and response of the infant to treatment. Evidence Quality: A; Strong Recommendation

Benefits	Inhibits further growth of bacterial pathogen. Cures infection. Reduces likelihood of morbidity. Contributes to antimicrobial stewardship.
Risks, harm, cost	Adverse reaction to antimicrobial. Interferes with infant's evolving microbiome. Accelerates emergence of antimicrobial resistance.
Benefit–harm assessment	Preponderance of benefit.
Key references	145, 155

mortality, discharge planning, and follow-up?

As a first step, questions 1, 2, and 5 could be partially answered by an effort to combine existing data sets from the large clinical and research groups publishing in this area. There are also international networks with similar foci on febrile infants. Although this would be challenging, it would still provide the shortest time to obtain the most accurate current assessment of risks.

It is clear that both the bacteriology and the technology involved in risk stratification and organism identification are evolving. Future research would benefit from a collaborative effort among researchers to define a common data set, with uniform definitions of elements and agreements to combine data for specific analyses. This effort could also lead to a model to answer question 10. As for question 12, it is now both methodologically and technologically feasible for a clinician to be able to enter a number of demographic, clinical, and laboratory data for a febrile infant and get the best estimate of risk for that patient.

LEAD AUTHOR

Robert H. Pantell, MD, FAAP

SUBCOMMITTEE ON FEBRILE INFANTS

Robert H. Pantell, MD, FAAP, Chair
Kenneth B. Roberts, MD, FAAP, Vice Chair
Charles R. Woods Jr, MD, MS, FAAP, Epidemiologist
William G. Adams, MD, FAAP
Carrie L. Byington, MD, FAAP
Benard P. Dreyer, MD, FAAP
Nathan Kuppermann, MD, MPH, FAAP, FACEP
Jane M. Lavelle, MD
Patricia S. Lye, MD, FAAP
Michelle L. Macy, MD, MS, FAAP
Flor M. Munoz, MD, MSc, FAAP
Carrie E. Nelson, MD, MS
Sean T. O'Leary, MD, MPH, FAAP
Stephen J. Pearson, MD, FAAP
Keith R. Powell, MD, FAAP
Jeb S. Teichman, MD, FAAP

WRITING GROUP

Robert H. Pantell, MD, FAAP, Lead
Kenneth B. Roberts, MD, FAAP, Co-lead
William G. Adams, MD, FAAP
Benard P. Dreyer, MD, FAAP, Ex Officio
Nathan Kuppermann, MD, MPH,

FAAP, FACEP
Sean T. O'Leary, MD, MPH, FAAP

STAFF

Kymika Okechukwu, MPA
Kristin Ingstrup
Jeremiah Salmon, MPH
Vanessa Shorte, MPH
Caryn Davidson, MA

ACKNOWLEDGMENTS

The committee acknowledges the generosity of individuals who graciously performed additional analyses from their published data sets and wisdom for this endeavor: Paul Aronson, MD, for the Febrile Young Infant Research Collaborative; Richard Bachur, MD (Division of Emergency Medicine, Boston Children's Hospital); Carrie Byington, MD (University of Utah and Intermountain Healthcare); Borja Gomez, MD (Pediatric Emergency Department, Cruces University Hospital); Tara Greenhow, MD (Kaiser Permanente Northern California); Nate Kuppermann, MD, MPH (PECARN); and Matthew Pantell, MD, MS (PROS). We also thank Eric Biondi, MD, for leading a series of focus groups of primary care and subspecialty pediatricians who scrutinized the guideline and provided feedback on implementation. We especially recognize Borja Gomez, MD (Pediatric Emergency Department, Cruces University Hospital). In a truly collegial fashion, he regularly ran subanalyses for us on his previously published data that helped us fill in many gaps and provide a more refined set of recommendations. The following groups provided feedback and suggestions that were incorporated during the process of development: AAP committees: Committee on Fetus and Newborn, Committee on Hospital Care, Committee on Infectious Diseases, Committee on Medical Liability and Risk Management, Committee on Pediatric Emergency Medicine, and Committee on Practice and Ambulatory Medicine; AAP council(s): Council on Quality Improvement and Patient Safety; AAP sections: Section on Administration and Practice Management, Section on Critical Care, Section on Emergency Medicine, Section on Epidemiology, Public Health, and Evidence, Section on Hospital Medicine, and Section on Infectious Diseases; other AAP groups: Family Partnerships Network, PROS, Quality Improvement Innovation Networks; and external groups: American Academy of Family Physicians, American College of Emergency Physicians, and Pediatric Infectious Diseases Society.

ABBREVIATIONS

AAP: American Academy of Pediatrics
AHRQ: Agency for Healthcare Research and Quality
ANC: absolute neutrophil count
AUC: area under the curve
CI: confidence interval
CRP: C-reactive protein
CSF: cerebrospinal fluid
ED: emergency department
GBS: group B *Streptococcus*
HSV: herpes simplex virus
IBI: invasive bacterial infection
IM: inflammatory marker
KAS: key action statement
LE: leukocyte esterase
LP: lumbar puncture
NPV: negative predictive value
PCR: polymerase chain reaction
PECARN: Pediatric Emergency Care Applied Research Network
PROS: Pediatric Research in Office Settings
RBC: red blood cell
RSV: respiratory syncytial virus
SBI: serious bacterial illness
SPA: suprapubic aspiration
UTI: urinary tract infection
WBC: white blood cell

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: Dr Byington is affiliated with BioFire and IDbyDNA. Dr Woods is affiliated with UpToDate. Dr Munoz-Rivas is affiliated with UpToDate, Moderna, and Pfizer; the other authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Roberts KB. Young, febrile infants: a 30-year odyssey ends where it started. *JAMA*. 2004;291(10):1261–1262
2. McCracken GH Jr. Group B streptococci: the new challenge in neonatal infections. *J Pediatr*. 1973;82(4):703–706
3. Caspe WB, Chamudes O, Louie B. The evaluation and treatment of the febrile infant. *Pediatr Infect Dis*. 1983;2(2):131–135
4. DeAngelis C, Joffe A, Wilson M, Willis E. Iatrogenic risks and financial costs of hospitalizing febrile infants. *Am J Dis Child*. 1983;137(12):1146–1149
5. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA*. 2001;285(16):2114–2120
6. Stockwell DC, Kirkendall E, Muething SE, Kloppenborg E, Vinodrao H, Jacobs BR. Automated adverse event detection collaborative: electronic adverse event identification, classification, and corrective actions across academic pediatric institutions. *J Patient Saf*. 2013;9(4):203–210

7. Makary MA, Daniel M. Medical error-the third leading cause of death in the US. *BMJ*. 2016;353:i2139

8. McCarthy PL, Sharpe MR, Spiesel SZ, et al. Observation scales to identify serious illness in febrile children. *Pediatrics*. 1982;70(5):802–809

9. Greene JW, Hara C, O'Connor S, Altemeier WA III. Management of febrile outpatient neonates. *Clin Pediatr (Phila)*. 1981;20(6):375–380

10. Dagan R, Powell KR, Hall CB, Menegus MA. Identification of infants unlikely to have serious bacterial infection although hospitalized for suspected sepsis. *J Pediatr*. 1985;107(6):855–860

11. Bonadio WA, Hagen E, Rucka J, Shallow K, Stommel P, Smith D. Efficacy of a protocol to distinguish risk of serious bacterial infection in the outpatient evaluation of febrile young infants. *Clin Pediatr (Phila)*. 1993;32(7):401–404

12. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med*. 1993;329(20):1437–1441

13. Baskin MN, Fleisher GR, O'Rourke EJ. Identifying febrile infants at risk for a serious bacterial infection. *J Pediatr*. 1993;123(3):489–490

14. Dagan R, Sofer S, Phillip M, Shachak E. Ambulatory care of febrile infants younger than 2 months of age classified as being at low risk for having serious bacterial infections. *J Pediatr*. 1988;112(3):355–360

15. Baraff LJ, Bass JW, Fleisher GR, et al; Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. *Pediatrics*. 1993;92(1):1–11

16. Bachur RG, Harper MB. Predictive model for serious bacterial infections among infants younger than 3 months of age. *Pediatrics*. 2001;108(2):311–316

17. Pantell RH, Newman TB, Bernzweig J, et al. Management and outcomes of care of fever in early infancy. *JAMA*. 2004;291(10):1203–1212

18. Kuppermann N, Dayan PS, Levine DA, et al; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN). A clinical prediction rule to identify febrile infants 60 days and younger at low risk for serious bacterial infections. *JAMA Pediatr*. 2019;173(4):342–351

19. Mintegi S, Bressan S, Gomez B, et al. Accuracy of a sequential approach to identify young febrile infants at low risk for invasive bacterial infection. *Emerg Med J*. 2014;31(e1):e19–e24

20. Gomez B, Mintegi S, Bressan S, Da Dalt L, Gervaix A, Lacroix L; European Group for Validation of the Step-by-Step Approach. Validation of the "Step-by-Step" approach in the management of young febrile infants. *Pediatrics*. 2016;138(2):e20154381

21. Young PC. The management of febrile infants by primary-care pediatricians in Utah: comparison with published practice guidelines. *Pediatrics*. 1995;95(5):623–627

22. Greenhow TL, Hung YY, Pantell RH. Management and outcomes of previously healthy, full-term, febrile infants ages 7 to 90 days. *Pediatrics*. 2016;138(6):e20160270

23. Jain S, Cheng J, Alpern ER, et al. Management of febrile neonates in US pediatric emergency departments. *Pediatrics*. 2014; 133(2):187–195

24. Aronson PL, Thurm C, Alpern ER, et al; Febrile Young Infant Research Collaborative. Variation in care of the febrile young infant <90 days in US pediatric emergency departments. *Pediatrics*. 2014;134(4):667–677

25. Greenhow TL, Hung YY, Herz AM. Changing epidemiology of bacteremia in infants aged 1 week to 3 months. *Pediatrics*. 2012;129(3). Available at: www.pediatrics.org/cgi/content/full/129/3/e590

26. Hui C, Neto G, Tsertsvadze A, et al. Diagnosis and management of febrile infants (0-3 months). *Evid Rep Technol Assess (Full Rep)*. 2012;205(205):1–297

27. Greenhow TL, Hung YY, Herz AM, Losada E, Pantell RH. The changing epidemiology of serious bacterial infections in young infants. *Pediatr Infect Dis J*. 2014;33(6):595–599

28. Levasseur KA, Stankovic C, Duffy E, Du W, Mahajan P. Prevalence of serious bacterial infections in return visits to the emergency department among infants aged 90 days or younger. *Pediatr Emerg Care*. 2014;30(10): 694–698

29. Hassoun A, Stankovic C, Rogers A, et al. *Listeria* and enterococcal infections in neonates 28 days of age and younger: is empiric parenteral ampicillin still indicated? *Pediatr Emerg Care*. 2014;30(4):240–243

30. Biondi E, Evans R, Mischler M, et al. Epidemiology of bacteremia in febrile infants in the United States. *Pediatrics*. 2013;132(6):990–996

31. Biondi EA, McCulloh R, Staggs VS, et al; American Academy of Pediatrics' Revise Collaborative. Reducing Variability in the Infant Sepsis Evaluation (REVISE): a national quality initiative. *Pediatrics*. 2019;144(3):e20182201

32. Leazer R, Perkins AM, Shomaker K, Fine B. A meta-analysis of the rates of *Listeria monocytogenes* and *Enterococcus* in febrile infants. *Hosp Pediatr*. 2016;6(4):187–195

33. Veesenmeyer AF, Edmonson MB. Trends in US hospital stays for listeriosis in infants. *Hosp Pediatr*. 2016;6(4): 196–203

34. Lyons TW, Garro AC, Cruz AT, et al; Herpes Simplex Virus Study Group of the Pediatric Emergency Medicine Collaborative Research Committee (PEM CRC). Performance of the modified Boston and Philadelphia criteria for invasive bacterial infections. *Pediatrics*. 2020;145(4):e20193538

35. Bergman DA, Mayer ML, Pantell RH, Finch SA, Wasserman RC. Does clinical presentation explain practice variability in the treatment of febrile infants? *Pediatrics*. 2006;117(3):787–795

36. Schroeder AR, Harris SJ, Newman TB. Safely doing less: a missing component of the patient safety dialogue. *Pediatrics*. 2011;128(6). Available at: www.pediatrics.org/cgi/content/full/128/6/e1596

37. Hernández-Bou S, Trenchs V, Vanegas MI, Valls AF, Luaces C. Evaluation of the bedside Quikread go® CRP test in the management of febrile infants at the emergency department. *Eur J Clin Microbiol Infect Dis*. 2017;36(7): 1205–1211

38. England JT, Del Vecchio MT, Aronoff SC. Use of serum procalcitonin in evaluation of febrile infants: a meta-analysis

of 2317 patients. *J Emerg Med*. 2014;47(6):682–688

39. Milcent K, Faesch S, Gras-Le Guen C, et al. Use of procalcitonin assays to predict serious bacterial infection in young febrile infants. *JAMA Pediatr*. 2016;170(1):62–69

40. Banerjee R, Teng CB, Cunningham SA, et al. Randomized trial of rapid multiplex polymerase chain reaction-based blood culture identification and susceptibility testing. *Clin Infect Dis*. 2015;61(7):1071–1080

41. Blaschke AJ, Heyrend C, Byington CL, et al. Rapid identification of pathogens from positive blood cultures by multiplex polymerase chain reaction using the FilmArray system. *Diagn Microbiol Infect Dis*. 2012;74(4):349–355

42. Salimnia H, Fairfax MR, Lephart PR, et al. Evaluation of the FilmArray blood culture identification panel: results of a multicenter controlled trial. *J Clin Microbiol*. 2016;54(3):687–698

43. Leber AL, Everhart K, Balada-Llasat JM, et al. Multicenter evaluation of biofire filmarray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. *J Clin Microbiol*. 2016;54(9):2251–2261

44. Krief WI, Levine DA, Platt SL, et al; Multicenter RSV-SBI Study Group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Influenza virus infection and the risk of serious bacterial infections in young febrile infants. *Pediatrics*. 2009;124(1):30–39

45. Mintegi S, Garcia-Garcia JJ, Benito J, et al. Rapid influenza test in young febrile infants for the identification of low-risk patients. *Pediatr Infect Dis J*. 2009;28(11):1026–1028

46. Bender JM, Taylor CS, Cumpio J, et al. Infants 1-90 days old hospitalized with human rhinovirus infection. *J Clin Lab Anal*. 2014;28(5):349–352

47. Levine DA, Platt SL, Dayan PS, et al; Multicenter RSV-SBI Study Group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. *Pediatrics*. 2004;113(6):1728–1734

48. Mahajan P, Browne LR, Levine DA, et al; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN). Risk of bacterial coinfections in febrile infants 60 days old and younger with documented viral infections. *J Pediatr*. 2018;203:86–91.e2

49. Nicholson EG, Avadhanula V, Ferlic-Stark L, Patel K, Gincoo KE, Piedra PA. The risk of serious bacterial infection in febrile infants 0-90 days of life with a respiratory viral infection. *Pediatr Infect Dis J*. 2019;38(4):355–361

50. Blaschke AJ, Korgenski EK, Wilkes J, et al. Rhinovirus in febrile infants and risk of bacterial infection. *Pediatrics*. 2018;141(2):e20172384

51. Ralston S, Hill V, Waters A. Occult serious bacterial infection in infants younger than 60 to 90 days with bronchiolitis: a systematic review. *Arch Pediatr Adolesc Med*. 2011;165(10):951–956

52. Doan Q, Enarson P, Kissoon N, Klassen TP, Johnson DW. Rapid viral diagnosis for acute febrile respiratory illness in children in the emergency department. *Cochrane Database Syst Rev*. 2014;(9):CD006452

53. Kadambari S, Braccio S, Ribeiro S, et al. Enterovirus and parechovirus meningitis in infants younger than 90 days old in the UK and Republic of Ireland: a British Paediatric Surveillance Unit study. *Arch Dis Child*. 2019;104(6):552–557

54. Nguyen DK, Friedlander S, Fleischman RJ, Zangwill KM. Length of stay and complications associated with febrile infants <90 days of age hospitalized in the United States, 2000-2012. *Hosp Pediatr*. 2018;8(12):746–752

55. Mahajan P, Kuppermann N, Suarez N, et al; Febrile Infant Working Group for the Pediatric Emergency Care Applied Research Network (PECARN). RNA transcriptional biosignature analysis for identifying febrile infants with serious bacterial infections in the emergency department: a feasibility study. *Pediatr Emerg Care*. 2015;31(1):1–5

56. Wilson MR, Sample HA, Zorn KC, et al. Clinical metagenomic sequencing for diagnosis of meningitis and encephalitis. *N Engl J Med*. 2019;380(24):2327–2340

57. Byington CL, Reynolds CC, Korgenski K, et al. Costs and infant outcomes after implementation of a care process model for febrile infants. *Pediatrics*. 2012;130(1). Available at: www.pediatrics.org/cgi/content/full/130/1/e16

58. Paxton RD, Byington CL. An examination of the unintended consequences of the rule-out sepsis evaluation: a parental perspective. *Clin Pediatr (Phila)*. 2001;40(2):71–77

59. Segal MR. Extending the elements of tree-structured regression. *Stat Methods Med Res*. 1995;4(3):219–236

60. Aronson PL, Shabanova V, Shapiro ED, et al; Febrile Young Infant Research Collaborative. A Prediction model to identify febrile infants ≤60 days at low risk of invasive bacterial infection. *Pediatrics*. 2019;144(1):e20183604

61. Powell EC, Mahajan PV, Roosevelt G, et al; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN). Epidemiology of bacteremia in febrile infants aged 60 days and younger. *Ann Emerg Med*. 2018;71(2):211–216

62. Ladhani SN, Henderson KL, Muller-Pebody B, Ramsay ME, Riordan A. Risk of invasive bacterial infections by week of age in infants: prospective national surveillance, England, 2010-2017. *Arch Dis Child*. 2019;104(9):874–878

63. Baker MD, Avner JR, Bell LM. Failure of infant observation scales in detecting serious illness in febrile, 4- to 8-week-old infants. *Pediatrics*. 1990;85(6):1040–1043

64. Nigrovic LE, Mahajan PV, Blumberg SM, et al; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN). The Yale Observation Scale score and the risk of serious bacterial infections in febrile infants. *Pediatrics*. 2017;140(1):e20170695

65. Roberts KB, Borzy MS. Fever in the first eight weeks of life. *Johns Hopkins Med J*. 1977;141(1):9–13

66. Kramer MS, Etezadi-Amoli J, Ciampi A, et al. Parents' versus physicians'

values for clinical outcomes in young febrile children. *Pediatrics*. 1994;93(5): 697–702

67. Madsen KA, Bennett JE, Downs SM. The role of parental preferences in the management of fever without source among 3- to 36-month-old children: a decision analysis. *Pediatrics*. 2006;117(4):1067–1076

68. De S, Tong A, Isaacs D, Craig JC. Parental perspectives on evaluation and management of fever in young infants: an interview study. *Arch Dis Child*. 2014;99(8):717–723

69. Aronson PL, Fraenkel L. Is shared decision-making the right approach for febrile infants? *Pediatrics*. 2017;140(3):e20170225

70. Aronson PL, Schaeffer P, Niccolai LM, Shapiro ED, Fraenkel L. Parents' perspectives on communication and shared decision making for febrile infants <60 days [published online ahead of print January 21, 2020]. *Pediatr Emerg Care*. doi:10.1097/PEC.0000000000001977

71. Aronson PL, Politi MC, Schaeffer P, et al. Development of an app to facilitate communication and shared decision-making with parents of febrile infants ≤ 60 days old. *Acad Emerg Med*. 2021;28(1):46–59

72. Djulbegovic B, Guyatt G. Evidence vs consensus in clinical practice guidelines. *JAMA*. 2019;322(8):725–726

73. Roberts KB; Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128(3):595–610. Reaffirmed December 2016

74. Eden J, Levit L, Berg A, Morton S, eds; Institute of Medicine. *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, DC: National Academies Press; 2011

75. Prymula R, Siegrist C-A, Chlibek R, et al. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. *Lancet*. 2009;374(9698):1339–1350

76. Byington CL, Enriquez FR, Hoff C, et al. Serious bacterial infections in febrile infants 1 to 90 days old with and without viral infections. *Pediatrics*. 2004;113(6):1662–1666

77. Schroeder AR, Newman TB, Wasserman RC, Finch SA, Pantell RH. Choice of urine collection methods for the diagnosis of urinary tract infection in young, febrile infants. *Arch Pediatr Adolesc Med*. 2005;159(10):915–922

78. Finnell SME, Carroll AE, Downs SM; Subcommittee on Urinary Tract Infection. Technical report—diagnosis and management of an initial UTI in febrile infants and young children. *Pediatrics*. 2011;128(3). Available at: www.pediatrics.org/cgi/content/full/128/3/e749

79. Glissmeyer EW, Korgenski EK, Wilkes J, et al. Dipstick screening for urinary tract infection in febrile infants. *Pediatrics*. 2014;133(5). Available at: www.pediatrics.org/cgi/content/full/133/5/e1121

80. Tzimenatos L, Mahajan P, Dayan PS, et al; Pediatric Emergency Care Applied Research Network (PECARN). Accuracy of the urinalysis for urinary tract infections in febrile infants 60 days and younger. *Pediatrics*. 2018;141(2):e20173068

81. Nelson JD, Peters PC. Suprapubic aspiration of urine in premature and term infants. *Pediatrics*. 1965;36(1):132–134

82. Marin JR, Shaikh N, Docimo SG, Hickey RW, Hoberman A. Videos in clinical medicine. Suprapubic bladder aspiration. *N Engl J Med*. 2014;371(10):e13

83. Kaufman J, Knight AJ, Bryant PA, Babl FE, Dalziel K. Liquid gold: the cost-effectiveness of urine sample collection methods for young precontinent children. *Arch Dis Child*. 2020;105(3): 253–259

84. Tran A, Fortier C, Giovannini-Chami L, et al. Evaluation of the bladder stimulation technique to collect midstream urine in infants in a pediatric emergency department. *PLoS One*. 2016;11(3):e0152598

85. Lavelle JM, Blackstone MM, Funari MK, et al. Two-step process for ED UTI screening in febrile young children: reducing catheterization rates. *Pediatrics*. 2016;138(1):e20153023

86. Schroeder AR, Chang PW, Shen MW, Biondi EA, Greenhow TL. Diagnostic accuracy of the urinalysis for urinary tract infection in infants <3 months of age. *Pediatrics*. 2015;135(6):965–971

87. Roberts KB. The diagnosis of UTI: liquid gold and the problem of gold standards. *Pediatrics*. 2015;135(6):1126–1127

88. Herreros ML, Tagarro A, García-Pose A, Sánchez A, Cañete A, Gili P. Performing a urine dipstick test with a clean-catch urine sample is an accurate screening method for urinary tract infections in young infants. *Acta Paediatr*. 2018;107(1):145–150

89. Roberts KB, Wald ER. The diagnosis of UTI: colony count criteria revisited. *Pediatrics*. 2018;141(2): e20173239

90. Herreros Fernández ML, González Merino N, Tagarro García A, et al. A new technique for fast and safe collection of urine in newborns. *Arch Dis Child*. 2013;98(1):27–29

91. Bachur R, Caputo GL. Bacteremia and meningitis among infants with urinary tract infections. *Pediatr Emerg Care*. 1995;11(5):280–284

92. Newman TB, Bernzweig JA, Takayama JI, Finch SA, Wasserman RC, Pantell RH. Urine testing and urinary tract infections in febrile infants seen in office settings: the Pediatric Research in Office Settings' Febrile Infant Study. *Arch Pediatr Adolesc Med*. 2002;156(1):44–54

93. Roman HK, Chang PW, Schroeder AR. Diagnosis and management of bacteremic urinary tract infection in infants. *Hosp Pediatr*. 2015;5(1):1–8

94. Blaschke AJ, Korgnski EK, Byington CL. Meningitis in well-appearing febrile infants aged 1–90 days. *Open Forum Infect Dis*. 2018;5(suppl 1):S133

95. Bonadio WA, Romine K, Gyuro J. Relationship of fever magnitude to rate of serious bacterial infections in neonates. *J Pediatr*. 1990;116(5): 733–735

96. Michelson KA, Neuman MI, Pruitt CM, et al; Febrile Young Infant Research Collaborative. Height of fever and invasive bacterial infection [published online August 20, 2020]. *Arch Dis Child*. 2021;106(6):594–596. doi:10.1136/archdischild-2019-318548

97. Gomez B, Bressan S, Mintegi S, et al. Diagnostic value of procalcitonin in well-appearing young febrile infants. *Pediatrics*. 2012;130(5):815–822

98. Woelker JU, Sinha M, Christopher NC, Powell KR. Serum procalcitonin concentration in the evaluation of febrile infants 2 to 60 days of age. *Pediatr Emerg Care*. 2012;28(5):410–415

99. Olaciregui I, Hernández U, Muñoz JA, Emparanza JI, Landa JJ. Markers that predict serious bacterial infection in infants under 3 months of age presenting with fever of unknown origin. *Arch Dis Child*. 2009;94(7):501–505

100. Gomez B, Diaz H, Carro A, Benito J, Mintegi S. Performance of blood biomarkers to rule out invasive bacterial infection in febrile infants under 21 days old. *Arch Dis Child*. 2019;104(6):547–551

101. Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt L. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. *Pediatr Infect Dis J*. 2007;26(8):672–677

102. Pulliam PN, Attia MW, Cronan KM. C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection. *Pediatrics*. 2001;108(6):1275–1279

103. Bonsu BK, Chb M, Harper MB. Identifying febrile young infants with bacteremia: is the peripheral white blood cell count an accurate screen? *Ann Emerg Med*. 2003;42(2):216–225

104. Cruz AT, Mahajan P, Bonsu BK, et al; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network. Accuracy of complete blood cell counts to identify febrile infants 60 days or younger with invasive bacterial infections. *JAMA Pediatr*. 2017;171(11):e172927

105. Gómez B, Mintegi S, Benito J, Egireun A, Garcia D, Astobiza E. Blood culture and bacteremia predictors in infants less than three months of age with fever without source. *Pediatr Infect Dis J*. 2010;29(1):43–47

106. Scarfone R, Murray A, Gala P, Balamuth F. Lumbar puncture for all febrile infants 29-56 days old: a retrospective cohort reassessment study. *J Pediatr*. 2017;187:200–205.e1

107. Leazer R, Erickson N, Paulson J, et al. Epidemiology of cerebrospinal fluid cultures and time to detection in term infants. *Pediatrics*. 2017;139(5):e20163268

108. Curfman AL, Glissmeyer EW, Ahmad FA, et al. Initial presentation of neonatal herpes simplex virus infection. *J Pediatr*. 2016;172:121–126.e1

109. Flagg EW, Weinstock H. Incidence of neonatal herpes simplex virus infections in the United States, 2006. *Pediatrics*. 2011;127(1). Available at: www.pediatrics.org/cgi/content/full/127/1/e1

110. Caviness AC, Demmler GJ, Almendarez Y, Selwyn BJ. The prevalence of neonatal herpes simplex virus infection compared with serious bacterial illness in hospitalized neonates. *J Pediatr*. 2008;153(2):164–169

111. American Academy of Pediatrics. Herpes simplex. In: Kimberlin DW, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:407–417

112. Long SS, Pool TE, Vodzak J, Daskalaki I, Gould JM. Herpes simplex virus infection in young infants during 2 decades of empiric acyclovir therapy. *Pediatr Infect Dis J*. 2011;30(7):556–561

113. Kotzbauer D, Frank G, Dong W, Shore S. Clinical and laboratory characteristics of disseminated herpes simplex virus infection in neonates. *Hosp Pediatr*. 2014;4(3):167–171

114. Sampath A, Maduro G, Schillinger JA. Infant deaths due to herpes simplex virus, congenital syphilis, and HIV in New York City. *Pediatrics*. 2016;137(4):e20152387

115. Morris SR, Bauer HM, Samuel MC, Gallagher D, Bolan G. Neonatal herpes morbidity and mortality in California, 1995-2003. *Sex Transm Dis*. 2008;35(1):14–18

116. Kotzbauer D, Andresen D, Doelling N, Shore S. Clinical and laboratory characteristics of central nervous system herpes simplex virus infection in neonates and young infants. *Pediatr Infect Dis J*. 2014;33(11):1187–1189

117. Meehan WP III, Bachur RG. Predictors of cerebrospinal fluid pleocytosis in febrile infants aged 0 to 90 days. *Pediatr Emerg Care*. 2008;24(5):287–293

118. Liesman RM, Strasburg AP, Heitman AK, Theel ES, Patel R, Binnicker MJ. Evaluation of a commercial multiplex molecular panel for diagnosis of infectious meningitis and encephalitis. *J Clin Microbiol*. 2018;56(4):e01927-e17

119. Fleischer E, Aronson PL. Rapid diagnostic tests for meningitis and encephalitis–Biofire. *Pediatr Emerg Care*. 2020;36(8):397–401

120. Nigrovic LE, Malley R, Agrawal D, Kuppermann N; Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Low risk of bacterial meningitis in children with a positive enteroviral polymerase chain reaction test result. *Clin Infect Dis*. 2010;51(10):1221–1222

121. Rittichier KR, Bryan PA, Bassett KE, et al. Diagnosis and outcomes of enterovirus infections in young infants. *Pediatr Infect Dis J*. 2005;24(6):546–550

122. Wallace SS, Lopez MA, Caviness AC. Impact of enterovirus testing on resource use in febrile young infants: a systematic review. *Hosp Pediatr*. 2017;7(2):96–102

123. Ramers C, Billman G, Hartin M, Ho S, Sawyer MH. Impact of a diagnostic cerebrospinal fluid enterovirus polymerase chain reaction test on patient management. *JAMA*. 2000;283(20):2680–2685

124. Dewan M, Zorc JJ, Hodinka RL, Shah SS. Cerebrospinal fluid enterovirus testing in infants 56 days or younger. *Arch Pediatr Adolesc Med*. 2010;164(9):824–830

125. Wylie TN, Wylie KM, Buller RS, Cannella M, Storch GA. Development and evaluation of an enterovirus D68 real-time reverse transcriptase PCR assay. *J Clin Microbiol*. 2015;53(8):2641–2647

126. Adler-Shohet FC, Cheung MM, Hill M, Lieberman JM. Aseptic meningitis in infants younger than six months of age hospitalized with urinary tract infections. *Pediatr Infect Dis J*. 2003;22(12):1039–1042

127. Schnadower D, Kuppermann N, Macias CG, et al; Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Sterile cerebrospinal fluid pleocytosis in young febrile infants with urinary tract infections. *Arch Pediatr Adolesc Med.* 2011;165(7):635–641

128. Doby EH, Stockmann C, Korgenski EK, Blaschke AJ, Byington CL. Cerebrospinal fluid pleocytosis in febrile infants 1-90 days with urinary tract infection. *Pediatr Infect Dis J.* 2013;32(9):1024–1026

129. Mintegi S, Benito J, Astobiza E, Capapé S, Gomez B, Eguireun A. Well appearing young infants with fever without known source in the emergency department: are lumbar punctures always necessary? *Eur J Emerg Med.* 2010;17(3):167–169

130. Nigrovic LE, Kuppermann N, Neuman MI. Risk factors for traumatic or unsuccessful lumbar punctures in children. *Ann Emerg Med.* 2007;49(6):762–771

131. Hanson AL, Ros S, Soprano J. Analysis of infant lumbar puncture success rates: sitting flexed versus lateral flexed positions. *Pediatr Emerg Care.* 2014;30(5):311–314

132. Pingree EW, Kimia AA, Nigrovic LE. The effect of traumatic lumbar puncture on hospitalization rate for febrile infants 28 to 60 days of age. *Acad Emerg Med.* 2015;22(2):240–243

133. Byington CL, Kendrick J, Sheng X. Normative cerebrospinal fluid profiles in febrile infants. *J Pediatr.* 2011;158(1):130–134

134. Neal JT, Kaplan SL, Woodford AL, Desai K, Zorc JJ, Chen AE. The effect of bedside ultrasonographic skin marking on infant lumbar puncture success: a randomized controlled trial. *Ann Emerg Med.* 2017;69(5):610–619.e1

135. Ayalin T, Lam SH. Ultrasound-assisted lumbar puncture in infants. *Acad Emerg Med.* 2011;18(4):e36

136. Pruitt CM, Neuman MI, Shah SS, et al; Febrile Young Infant Research Collaborative. Factors associated with adverse outcomes among febrile young infants with invasive bacterial infections. *J Pediatr.* 2019;204:177–182.e1

137. King RL, Lorch SA, Cohen DM, Hodinka RL, Cohn KA, Shah SS. Routine cerebrospinal fluid enterovirus polymerase chain reaction testing reduces hospitalization and antibiotic use for infants 90 days of age or younger. *Pediatrics.* 2007;120(3):489–496

138. Aronson PL, Wang ME, Nigrovic LE, et al; Febrile Young Infant Research Collaborative. Time to pathogen detection for non-ill versus ill-appearing infants ≤60 days old with bacteremia and meningitis. *Hosp Pediatr.* 2018;8(7):379–384

139. Alpern ER, Kuppermann N, Blumberg S, et al; Pediatric Emergency Care Applied Research Network (PECARN). Time to positive blood and cerebrospinal fluid cultures in febrile infants ≤60 days of age. *Hosp Pediatr.* 2020;10(9):719–727

140. Biondi EA, Mischler M, Jerardi KE, et al; Pediatric Research in Inpatient Settings (PRIS) Network. Blood culture time to positivity in febrile infants with bacteremia. *JAMA Pediatr.* 2014;168(9):844–849

141. Kumar Y, Qunibi M, Neal TJ, Yoxall CW. Time to positivity of neonatal blood cultures. *Arch Dis Child Fetal Neonatal Ed.* 2001;85(3):F182–F186

142. Vamsi SR, Bhat RY, Lewis LE, Vandana KE. Time to positivity of blood cultures in neonates. *Pediatr Infect Dis J.* 2014;33(2):212–214

143. Jardine L, Davies MW, Faoagali J. Incubation time required for neonatal blood cultures to become positive. *J Paediatr Child Health.* 2006;42(12):797–802

144. Lefebvre CE, Renaud C, Chartrand C. Time to positivity of blood cultures in infants 0 to 90 days old presenting to the emergency department: is 36 hours enough? *J Pediatric Infect Dis Soc.* 2017;6(1):28–32

145. Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021 Report of the Committee on Infectious Diseases.* 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021

146. Velasco R, Gomez B, Benito J, et al. Accuracy of PECARN rule for predicting serious bacterial infection in infants with fever without a source. *Arch Dis Child.* 2020;106(2):143–148

147. Nguyen THP, Young BR, Poggel LE, Alabaster A, Greenhow TL. Roseville protocol for the management of febrile infants 7–60 days. *Hosp Pediatr.* 2020;11(1):52–60

148. Bhansali P, Wiedermann BL, Pastor W, McMillan J, Shah N. Management of hospitalized febrile neonates without CSF analysis: a study of US pediatric hospitals. *Hosp Pediatr.* 2015;5(10):528–533

149. Wang ME, Biondi EA, McCulloh RJ, et al. Testing for meningitis in febrile well-appearing young infants with a positive urinalysis. *Pediatrics.* 2019;144(3):e20183979

150. Bonadio W, Maida G. Urinary tract infection in outpatient febrile infants younger than 30 days of age: a 10-year evaluation. *Pediatr Infect Dis J.* 2014;33(4):342–344

151. Pantell RH, Roberts KB, Greenhow TL, Pantell MS. Advances in the diagnosis and management of febrile infants: challenging tradition. *Adv Pediatr.* 2018;65(1):173–208

152. Carmon L, Goldbart A, Greenberg D, Ben-Shimol S. Serious bacterial infections in hospitalized febrile infants in the first and second months of life. *Pediatr Infect Dis J.* 2017;36(10):924–929

153. Schnadower D, Kuppermann N, Macias CG, et al; American Academy of Pediatrics Pediatric Emergency Medicine Collaborative Research Committee. Febrile infants with urinary tract infections at very low risk for adverse events and bacteremia. *Pediatrics.* 2010;126(6):1074–1083

154. Young BR, Nguyen THP, Alabaster A, Greenhow TL. The prevalence of bacterial meningitis in febrile infants 29-60 days with positive urinalysis. *Hosp Pediatr.* 2018;8(8):450–457

155. Hoberman A, Wald ER, Hickey RW, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics.* 1999;104(1, pt 1):79–86