Evaluation of Child with Fever Without Source

Review of Literature and Update

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KEYWORDS

• Fever • Serious bacterial infection • Fever without source • Tissue culture

KEY POINTS

- Fever is a common reason for visits to the emergency department for children 36 months of age and younger.
- Although laboratory testing is routinely used and hospitalization is frequent, especially for the young febrile infant, there is substantial variation in their evaluation and management.
- This variation in practice has significant implications in terms of cost and, potentially, safety, owing to possible iatrogenic overuse of invasive procedures (lumbar punctures), empiric antibiotics, and unnecessary hospitalizations.
- Routinely used screening tests in the evaluation of serious bacterial infection (SBI) in young febrile infants are inaccurate, and cannot be relied upon to distinguish between those with bacterial and those with nonbacterial infections.
- Newer pathogen-detection techniques are likely to evolve rapidly and to affect the way SBI as an entity is evaluated.

INTRODUCTION

Fever is a common complaint in infants and children, and represents 10.5% to 25% of pediatric emergency department (ED) visits.[1–3] Although most febrile children have self-limited viral infections, a small but not insignificant proportion (especially infants 3 months of age and younger) will have serious bacterial infection (SBI), including bacteremia, bacterial meningitis, urinary tract infection (UTI), pneumonia, septic arthritis, osteomyelitis, and enteritis.[4,5] Incidence of SBI has been estimated at 6%

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to 10% in infants younger than 3 months and 5% to 7% of children between 3 and 36 months of age.[6,7] However, during the past 2 decades, routine vaccinations against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* have significantly changed the epidemiology of SBI. The evaluation of the young febrile infant is more challenging because the infant's immune system is relatively immature during the first 2 to 3 months of life; chemotactic responses such as opsonin activity, macrophage function, and neutrophil activity are decreased, making the infant more susceptible to bacterial infection.[8] The risk of SBI decreases with age, and increases with height and duration of fever. The evaluation and management of febrile infants and children who are ill-appearing or have an evident focus of infection is straightforward. It is the otherwise well-appearing subset of febrile infants and children without a localizing focus that poses a diagnostic dilemma. Febrile illness in children results in significant parental anxiety. Management decisions about febrile children are further complicated by the fact that parents and physicians weigh the risks and costs differently.[9] Despite many studies aimed at identifying individual biomarkers or a combination of clinical and laboratory tests, to date there is no single test or combinations of tests and clinical findings that have characteristics adequate to reliably identify SBI in the febrile child. It is, therefore, not surprising that the clinical priority, recently identified by emergency physicians, is the need for development of clinical decision rules for the evaluation and management of the febrile child younger than 36 months.[10]

This article reviews the literature on the evaluation and management of the febrile child, and comments on recent advances that may have potential to change the paradigm for detection of pathogens. The authors discuss evaluation of the febrile child in 2 age groups, febrile infants 3 months or younger and those between 3 and 36 months of age.

OCCULT BACTEREMIA

Occult bacteremia (OB) is defined as the presence of bacteria in the blood of an otherwise well-appearing febrile child in the absence of an identifiable focal bacterial source of infection. This term was introduced in the 1970s when bacteremia was identified in febrile children (3–36 months) who were at risk for developing systemic or focal infections such as sepsis, meningitis, and osteomyelitis, despite a relatively benign clinical appearance, but.[11] In the prevaccine era, the prevalence of OB was 2.4% to 11.6% in all children with fever without source (FWS), with *Streptococcus pneumoniae* accounting for most cases (50%–90%); 3% to 25% were due to *Haemophilus influenzae* type b, with the remainder due to *Salmonella* species and *Neisseria meningitidis*.[12,13]

The impact of conjugate vaccines has been highest in the 3- to 36-month group of well-appearing febrile children. Not only has the overall incidence of bacteremia dropped to 0.17% to 0.36%, the nonvaccinated population has also benefited through the phenomenon known as "herd protection." Indeed, in well-appearing children 3 to 36 months of age with FWS, overall OB rates of less than 0.5% have been reported in studies with pneumococcal conjugate vaccine (PCV7) coverage in the general population of approximately 80%.[14,15] Although there are surveillance data suggesting a relative increase in infections caused by a limited number of nonvaccine serotypes, particularly serotype 19A, which is often multidrug resistant, the majority of cases of bacteremia are due to *Streptococcus pyogenes*, *Enterococcus* spp, *N meningitidis*, non–type b *H influenzae*, *Escherichia coli*, *Moraxella. catarrhalis*, *Salmonella* spp, and *Staphylococcus aureus*.[14–17]

A shift in epidemiology of OB has also been identified in febrile infants younger than 3 months, largely attributable to advances in medical practices, prenatal screening,

and intrapartum chemoprophylaxis against Group B *Streptococcus* (GBS). A large epidemiologic study on 4122 infants 1 week to 3 months of age revealed that *E coli* accounted for 56% of all cases of bacteremia, followed by GBS (21%), *S aureus* (8%), *Streptococcus viridans* (3%), *S pneumoniae* (3%), *Klebsiella* (2%), and *Salmonella* (2%). There were no cases of *Listeria monocytogenes* bacteremia, or meningococcemia, with only 1 case of enterococcal bacteremia.[18]

URINARY TRACT INFECTION

Pediatric UTIs account for 0.7% of physician office visits and 5% to 14% of ED visits by children annually.[19] The overall prevalence of UTI in febrile infants younger than 24 months has been estimated as from 5% to 7%, however, certain subgroups of children are at higher risk for UTIs.[20,21] In 2008, Shaikh and colleagues[21] pooled estimates for 18 studies that examined the rate of culture-positive bacteriuria in febrile infants, breaking down the results by age group and sex. There was a prevalence of 7.5% and 8.7%, respectively, among febrile girls and boys younger than 3 months, whereas corresponding numbers for febrile children aged 3 to 12 months were 8.3% and 1.7%, respectively. Among febrile children aged 12 to 24 months, only data for girls were available, suggesting a rate of 2.1%. UTI rates in uncircumcised febrile male infants younger than 3 months was the highest for any group, at 20.1% (95% confidence interval [CI] 16.8–23.4), and was 10 times higher than their circumcised counterparts who had the lowest rates. UTI rates were significantly higher among white infants than among black infants (8.0% vs 4.7%).

The updated 2011 American Academy of Pediatrics guidelines recommend aggressive diagnosis, treatment, and investigation of possible UTI, with the goal of reducing renal scarring and, thus, kidney damage.[20] It provides an initial algorithm to estimate the risk of UTI in febrile children aged 2 to 24 months that is based on clinical and demographic characteristics. The major risk factor for febrile infant boys is whether they are circumcised. The probability of UTI ($\leq$1% or $\leq$2%) can be estimated according to the number of risk factors present, namely, non–black race, temperature of at least 39°C, fever for more than 24 hours, and absence of another source of infection. In girls, risk factors such as white race, age under 12 months, temperature greater than 39°C, fever longer than 2 days, and absence of another source of infection will determine the probability or likelihood of UTI, with each additional risk factor increasing the probability.[22] Diagnosis of UTI requires the presence of both pyuria and bacteruria and at least 50,000 colonies per mL of a single uropathogenic organism in an appropriately collected (straight catheterization) specimen of urine.[20] It should be noted that the guidelines exclude infants 2 months of age and younger.

MENINGITIS

Incidence of pneumococcal meningitis in children younger than 2 years has decreased by 64% following widespread use of PCV7 vaccine as reported from an extensive review of the Nationwide Inpatient Sample (1994–2004).[23,24] The investigators also report a 17.5%, 54%, and 50% decrease in meningitis due to GBS, meningococcus, and *H influenzae*. Most experts do not recommend obtaining cerebrospinal fluid (CSF) studies in the evaluation of an alert, febrile child 3 to 36 months of age with a normal neurologic examination. Performance of lumbar puncture continues to vary in the younger febrile infant, and no firm recommendations can be made because of paucity of large and geographically diverse studies in this age group.[25]

PNEUMONIA

The diagnosis of pneumonia in the pediatric population remains challenging. Despite its common occurrence, accurate diagnosis of bacterial pneumonia is difficult because most lower respiratory tract infections are viral in etiology, and findings on routine chest radiographs are nondiagnostic (ie, it is often difficult to ascribe cause, bacterial or nonbacterial, on "positive" chest radiograph findings in the absence of positive cultures). Indeed, blood cultures are rarely positive, and obtaining sputum/pleural fluid aspirates for etiologic diagnosis is impractical. Moreover, there is substantial variation in interpretation of chest radiographs among ED physicians and even among trained radiologists.[25]

Similarly to bacteremia and meningitis, the incidence of pneumococcal pneumonia has reduced substantially (a 65% decline in hospital admissions for pneumococcal pneumonia and a 39% decline in admissions for pneumonia in all pediatric age groups). In an extensive analysis, Murphy and colleagues[26] reveal the following factors that increase the likelihood of a radiographic pneumonia: increasing duration of fever (likelihood ratio [LR+] 1.62 for fever longer than 3 days and LR+ 2.24 for fever longer than 5 days), presence of cough (LR+ 1.24), prolonged cough (>10 days, LR+ 2.25), and a white blood cell (WBC) count greater than 20,000/mm^3 (LR+ 2.17). A different study revealed that the incidence of pneumonia increased with age (odds ratio [OR] 2.62 for infants >12 months; 95% CI 1.04–6.60), C-reactive protein (CRP) level greater than 100 mg/L (OR 3.18; 95% CI 1.19–8.51), and absolute neutrophil count greater than 20 $\times$ 10^9/L (OR 3.52; 95% CI 1.37–9.06).[27]

In summary, pneumonia as an SBI in the absence of signs and symptoms of lower respiratory tract involvement is highly unlikely, and routine chest radiographs should not be performed.

FEBRILE CHILDREN WITH CONFIRMED VIRAL ILLNESS

Because fever in most febrile children will have a viral source, identification of the presence of virus by rapid bedside tests have been incorporated for both epidemiologic and management purposes.[28] The advent of rapid testing for viral pathogens has resulted in changes in the management of febrile infants younger than 90 days, as well as older febrile infants and children, including decreased ancillary testing, decreased use of antibiotics, and shorter hospital stays.[29,30] Febrile children with documented viral infections had a lower prevalence of SBI, with the investigators recommending that blood cultures may not be necessary in their evaluation.[31] In a recent study on children aged 2 to 36 months, 1 or more viruses were detected in 76% (n = 75) of children with FWS. Adenovirus, human herpesvirus 6, enterovirus, and parechoviruses accounted for 57% of all viruses.[28] It was concluded that future studies should explore the utility of testing for the implicated viruses, as better recognition of viruses that cause undifferentiated fever in young children may help limit unnecessary antibiotic use.

However, detection of specific viral infections (especially respiratory syncytial virus [RSV]) has been shown to decrease, but not completely eliminate the risk of SBIs in very young febrile infants, especially those 60 days of age and younger. One multicenter prospective study of 1248 febrile infants 60 days and younger revealed that there was no significant difference in the prevalence of bacteremia and meningitis in febrile infants with documented RSV infection than in those without RSV (1.1% vs 2.3%, risk difference: 1.2%; 95% CI: 0.4%–2.7%).[32] Similar results were demonstrated by the same investigators when rates of SBI were compared among febrile infants with and without influenza infection.[33] An evidence-based review conducted by the Agency for Healthcare Research and Quality (AHRQ) demonstrated a

significantly reduced risk of SBI among infants who tested positive for the presence of viral infection or clinical bronchiolitis when compared with infants who tested negative for the presence of viral infection or bronchiolitis, but cautioned that this finding may not be applicable to neonates.[34]

In summary, identification of a virus in a febrile child may help clinicians to reduce the need for further testing to identify a bacterial cause in the older febrile child. Clinicians should consider obtaining urine studies to rule out UTIs, especially in young children (females <2 years old, uncircumcised males <1 year old, and circumcised males <6 months old), and as part of a comprehensive evaluation for SBI including blood and CSF samples in febrile infants 60 days of age and younger.

ROLE OF SCREENING TESTS

To date there is no ideal test for identifying young, febrile children with occult SBIs, although much research has been performed on complete WBC count, and differential counts including absolute neutrophil count (ANC), band counts, CRP, interleukins (IL) (IL-6, IL-1, and IL-8), and serum procalcitonin (PCT).[35]

Complete WBC count continues to remain the most commonly used screening test for SBI and various algorithms suggest a cutoff value between 15,000 and 20,0000/mm^3 to stratify febrile infants as low or high risk.[36] However, the test characteristics remain suboptimal, with sensitivities ranging from 50% to 69% and specificity from 53% to 80%.[37] Studies in the post-PCV7 era have shown that a WBC count of greater than 15,000/mm^3 yields a positive predictive value of only 1.5% to 3.2%.[34] It is important to recognize that traditionally accepted WBC cutoffs may no longer be relevant as the epidemiology of OB shifts away from *S pneumoniae*.[38,39] Zaidi and colleagues[39] retrospectively reviewed nontyphi *Salmonella* bacteremia and showed that 54% had a median WBC count of 10,000/mm^3. Furthermore, WBC counts by themselves are of limited value for "ruling in" SBI (positive likelihood ratio 0.87–2.43) and for ruling out SBI (negative likelihood ratio 0.61–1.14).[40]

Both CRP and serum PCT have been studied in the evaluation of the febrile child. Several studies have demonstrated that serum PCT levels increase more rapidly in bacterial infections when compared with CRP and other biomarkers such as the interleukins. Furthermore, serum PCT levels correlate with severity of disease and mortality.[35,41] Studies on the accuracy of PCT in screening febrile children for SBI in the ED setting have revealed inconsistent results. Two separate studies demonstrated that PCT was the single best laboratory screening test when compared with IL-6, IL-8, and IL-1 receptor antagonists, CRP, and other routinely used laboratory screening tests for distinguishing those with viral and bacterial infections.[42,43] By contrast, the findings of another study of 72 febrile children 1 to 36 months of age suggest that the diagnostic accuracy of PCT, CRP, and WBC are comparable with that of clinical scoring (Yale Observational Scale [YOS]) and do not change posttest probabilities to a clinically useful extent.[44] Evidence-based reviews of published studies on the use of PCT as a screening test for SBI in febrile children younger than 3 years concluded that PCT is still not sufficiently sensitive to be used as a single screening tool to exclude the possibility of SBI.[45–47] PCT seems promising and may have some utility in identifying SBI, but it is not clear if the marginal benefit over routinely obtained screening tests is sufficient to be included in the evaluation of the febrile child.

ROLE OF PREDICTION RULES

Clinical-decision rules or prediction rules use clinical findings (history, physical examination, and test results) to make a diagnosis or predict outcomes, and when

appropriately applied can "change clinical behavior and reduce unnecessary costs while maintaining quality of care and patient satisfaction."[48] Reliance on clinical examination alone is insufficient, as demonstrated by the suboptimal performance of the YOS in very young febrile infants. Craig and colleagues[49] evaluated 40 clinical features to construct a multivariate model to identify SBI in 15,781 febrile children younger than 5 years, and demonstrated that clinical signs and symptoms contribute differently to predicting the risk of SBI. Overall ill/unwell appearance was found to be the strongest diagnostic marker for all SBI. Other clinical parameters such as raised temperature, no fluid intake in the previous 24 hours, increased capillary refill time, and chronic disease were also predictive of SBI. Bachur and Harper[6] developed a model that sequentially used 4 clinical parameters to define high-risk patients: positive urinalysis, WBC count greater than 20,000/mm^3 or less than 4100/mm^3, temperature greater than 39.6°C, and age younger than 13 days. The sensitivity of the model for SBI is 82% (95% CI 78%–86%) and the negative predictive value is 98.3% (95% CI 97.8%–98.7%). The negative predictive value for bacteremia or meningitis is 99.6% (95% CI 99.4%–99.8%).

Some of the more well-known algorithms/rules in the evaluation of the febrile infant are described in **Table 1**. A comprehensive review was recently conducted by the AHRQ, which concludes that the 3 more well-known rules (ie, Boston, Philadelphia, and Rochester) were fairly accurate in identifying a low-risk group for SBI in infants younger than 3 months.[34] Recently, biological markers such as PCT and CRP have been incorporated along with other routine screening tests in patient-evaluation algorithms. For instance, the "lab-score" combines PCT, CRP, and urine dipstick. It has been derived and validated for predicting SBIs in children 7 days to 36 months of age with FWS.[50,51] **Table 2** details the elements and test characteristics of a lab-score cutoff of 3 or greater in predicting the risk of SBI by age. In their validation article, the Bressan and colleagues[51] compared the characteristics of the lab-score with individual biomarkers, and demonstrated superior performance of combined lab-score over individual biomarkers. Another study investigated the accuracy and usefulness of the lab-score in predicting SBI in well-appearing infants younger than 3 months with FWS, and found it more useful for ruling in, rather than ruling out SBI.[52]

This approach, however, has significant implications in terms of cost and, potentially, safety, because of the possible iatrogenic overuse of invasive procedures (lumbar punctures), empiric antibiotics, and unnecessary hospitalizations.[53,54] Considerable debate exists, and much has been written, about these guidelines because: (1) most research studies pertaining to febrile infants have been conducted in a single or small groups of academic centers; (2) many studies have used retrospective study designs and different inclusion criteria (eg, with respect to age and temperature cutoffs to define fever), and different laboratory criteria for distinguishing high-risk from low-risk infants; and (3) increasing evidence questions the discriminatory ability of commonly used screening tests in young febrile infants. Consequently, variation continues to exist, and multiple laboratory testing is common, in the evaluation of febrile infants. Variation in approach is determined by several factors, including the clinical setting (academic vs community EDs vs general pediatric practices) and clinician training (emergency medicine vs general pediatrics vs pediatric emergency medicine).[6,7,53]

CULTURES AS REFERENCE STANDARDS: TIME TO REEVALUATE OUR APPROACH?

Cultures of relevant tissue fluids are a part of the evaluation for SBI and constitute the current reference standard. However, reliance on blood cultures is problematic for

Table 1
Commonly used algorithms and pathways for risk stratification in management of febrile infants 3 months of age and younger

Low-Risk Criteria	Boston[a]	Philadelphia[a]	Rochester[a]	Pittsburgh Criteria	Boston Predictive Model	Milwaukee[a] Criteria
Age (d)	28–89	29–56	0–60	<60	<90	28–56
Temperature (°C)	≥38.0	≥38.2	≥38.0	>38.0	>39.6	≥38.0
Clinical appearance or YOS	Well	Well	Well	No	No	Well
CBC	>5000 or <20,000	<15,000	>5000 or <15,000	>5000 or <15,000	>20,000 or <40,100	<15,000
Band counts	NA	<0.2 B:N ratio	<1500	<1500	NA	NA
UA	<10 WBC/hpf	<10 WBC/hpf	<10 WBC/hpf	Enhanced WBC <9	>5/Dip(+)	UA <5–10 WBC/hpf (no bacteria, negative LE/nitrite)
Urine Gram stain	NA	Yes	NA	Yes	NA	NA
CSF	<10 WBC/mm^3	<8 WBC/mm^3	Not required	<5, (–) GM	NA	<10 WBC/mm^3
Stools	If diarrhea	If diarrhea	If diarrhea	<5	NA	NA
Chest radiograph	If done	All	If done	Yes	NA	If done

Abbreviations: B:N, Bands: Neutrophil; CBC, complete blood count; CSF, cerebrospinal fluid; GM, gram stain; hpf, high-power field; LE, Leukocyte Esterase; NA, no data available; UA, urinalysis; WBC, white blood cells; YOS, Yale Observational Scale.

[a] Reliable caretaker and follow-up required within 24 hours if patient is discharged home from the ED.

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Table 2
Lab-score and its test characteristics

Predictors	Cutoff Values	Points
Procalcitonin (ng/mL)	<0.5	0
	>0.5	2
	>2	4
C-reactive protein (mg/L)	<40	0
	40–99	2
	≥100	4
Urine dipstick (leukocyte esterase and/or nitrite)	Negative	0
	Positive	1

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR− (95% CI)
Lab-score ≥3 (N = 406)	86 (77–92)	83 (79–87)	60 (51–68)	95 (92–97)	5.1 (3.9–6.6)	0.17 (0.1–0.28)
Age <3 mo (n = 106)	78 (59–89)	90 (81–95)	72 (54–85)	92 (84–96)	7.7 (3.9–15.3)	0.25 (0.12–0.50)
Age 3–12 mo (n = 138)	79 (62–90)	85 (78–91)	59 (43–73)	94 (87–97)	5.4 (3.3–8.8)	0.24 (0.12–0.50)
Age >12 mo (n = 162)	97 (86–100)	77 (69–84)	55 (43–67)	99 (94–100)	4.2 (3.1–5.8)	0.04 (0.01–0.25)

Abbreviations: CI, confidence interval; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

Data from Lacour AG, Zamora SA, Gervaix A. A score identifying serious bacterial infections in children with fever without source. Pediatr Infect Dis J 2008;27:654–6; and Galetto-Lacour A, Zamora SA, Andreola B, et al. Validation of a laboratory risk index score for the identification of severe bacterial infection in children with fever without source. Arch Dis Child 2010;95:968–73.

several reasons. In the postconjugate vaccine era, a majority of blood cultures are false positive and reflect the growth of "contaminants." The likelihood of obtaining false-positive cultures increased after the introduction of PCV7 from 62.5% to 87.8% (OR 4.3; 95% CI 1.44–13.38).[55] Other studies have revealed that contaminants are 10 times more likely than pathogens to be isolated in the evaluation of a febrile child.[14,15] False-positive cultures are also a common occurrence in young febrile infants, as demonstrated by a study of 4255 blood cultures in infants younger than 3 months, which revealed that 73% of positive culture results were contaminants, potentially leading to increased treatments, iatrogenic complications, and costs.[18] The ability of culture techniques to identify true pathogens depends on various factors including time between sample collection and incubation, volume of blood collected, the duration inoculated blood-culture bottles are left at room temperature, the presence of fastidious pathogens that grow slowly or require complex culture media, and prior antimicrobial therapy. Also, a significant number of clinically important microbial pathogens remain unrecognized because they are resistant to cultivation in the laboratory.[56] Thus the false-negative rate of cultures is largely unknown, further limiting their usefulness in the clinical realm. Another consideration in the clinical use of blood-culture testing is the time to growth of pathogens, which frequently leads to hospitalization or use of long-acting antibiotics until lack of growth can be confirmed. In addition, blood cultures may also be false negative if bacteremia is transient or intermittent. Indeed, the false-positive and false-negative rates of cultures will affect the duration and cost of care.

Experts suggest that it may no longer be cost-effective to obtain routine blood cultures in the evaluation of SBI in febrile children between 3 and 36 months of age. Furthermore, newer pathogen-detection techniques or quantification of the host response as an alternative approach for disease identification has been investigated to overcome the limitations of cultures. Although exhaustive review of recent advances in microbiological detection is beyond the scope of this article, 2 technologies need to be highlighted. First, application of molecular assays for pathogen identification, the promising universal polymerase chain reaction (PCR) assay based on the detection of the bacterial 16S ribosomal RNA gene, has shown some promise but does have its limitations. An integrated diagnostic platform, the "Film array," a multiplex PCR system that fully automates detection of multiple organisms from a single sample with a turnaround time of approximately 1 hour, is being investigated.[57,58] Second, it is now possible to detect the presence of infection by assessing the specific host responses, as different pathogens induce distinct transcriptional "biosignatures" in the RNA of blood leukocytes that can be reliably measured by microarray analysis using small blood samples. Recent data reveal that pathogens can be detected with approximately 95% accuracy, and this technique is currently being investigated in the context of the febrile infant.[59]

MANAGEMENT OF THE FEBRILE CHILD WITH FWS

Management of Febrile Child 3 to 36 Months Old

No single algorithm, guideline, or combination of laboratory screening tests can be recommended in the evaluation of SBI in this age group because of the impact of conjugate vaccines on the epidemiology of SBI and the suboptimal test characteristics of the screening biomarkers. Clinicians should perform urine analysis and cultures on appropriately collected samples, especially in febrile female children younger than 24 months, uncircumcised males younger than 12 months, and circumcised males younger than 6 months. Chest radiographs should not be obtained in the absence

of signs and symptoms suggestive of a lower respiratory tract involvement. Blood and CSF studies should be obtained on individual cases based on history, physical examination, and social situation.

Management of Febrile Infant 3 Months and Younger

Clinicians have typically subdivided febrile infants into 2 categories: febrile neonates (28 days or 4 weeks and younger) and febrile infants 28 to 90 days old.

Febrile neonate (28 days or 4 weeks and younger)

The management of febrile neonates is less controversial because of the relative immaturity of their immune system; these infants have a higher incidence of SBI compared with other age categories and their examination is unreliable. Thus, even for a well-appearing febrile neonate, most experts would advocate a complete sepsis evaluation including a lumbar puncture and hospitalization for parenteral antimicrobial therapy pending the results of the assessment. If herpes simplex virus is suspected on clinical or epidemiologic grounds, acyclovir therapy should be strongly considered. Results of rapid viral testing do not alter the management in this age group.

Febrile infant between 4 weeks and 12 weeks old

The authors anticipate that the evaluation for SBI in this age group will continue to vary in its comprehensiveness and application based on practice setting, training of providers, and the availability of ancillary tests including comprehensive rapid viral panels and screening tests such as PCT and CRP. At present, no single algorithm or treatment pathway can be recommended, but readers are directed to a comprehensive evidence-based analysis conducted by the AHRQ that details the shortcomings of various evaluation approaches. It is likely that the younger febrile infant (ie, those between 4 weeks and 8 weeks of age) will obtain analysis of blood and urine with or without CSF, empiric parenteral third-generation cephalosporins, and may or may not be hospitalized until culture negative. Given the higher prevalence of UTI, urine analysis and culture should be performed via either bladder catheterization or suprapubic aspiration. Clinicians could choose to include a complete blood count, CRP, and PCT along with results of viral studies when available to make treatment and disposition decisions for infants between 4 weeks and 12 weeks of age. It is imperative that a reliable follow-up within 24 hours is assured among those febrile infants who are managed on an outpatient basis, especially those who do not get a CSF analysis. It is likely that individual institutions will modify currently available guidelines/algorithms to reduce variation in care. A variety of these guidelines are available in the peer-reviewed literature.

SUMMARY

Fever is a common reason for ED visits by children 36 months and younger. Although laboratory testing is routinely used and hospitalization is frequent, especially in the young febrile infant, there is substantial variation in their evaluation and management. In practice, however, this variation has significant implications in terms of cost and, potentially, safety because of possible iatrogenic overuse of invasive procedures (lumbar punctures), empiric antibiotics, and unnecessary hospitalizations. Considerable debate exists, and much has been written about, clinical-evaluation guidelines because: (1) most research studies pertaining to febrile infants have been conducted in a single center or small groups of academic centers; (2) many studies have used retrospective study designs, different inclusion criteria (eg, with respect to age and temperature cutoffs to define fever), and different laboratory criteria for distinguishing

high-risk from low-risk infants; and (3) increasing evidence questions the discriminatory ability of commonly used screening tests in young febrile infants. Routinely used screening tests in the evaluation of young febrile infants for SBIs are inaccurate, and cannot be relied on to distinguish between those with bacterial and those with nonbacterial infections. The value of newer screening tests, such as PCT levels, in this population is not clear, and needs to be evaluated in a large, multicenter study including sufficient numbers of patients to obtain precise estimates of test accuracy. Finally, newer pathogen-detection techniques are likely to evolve rapidly and to affect the way SBI as an entity is evaluated. Given the current state of research and epidemiology of SBI in well-appearing febrile children, a complete evaluation for SBI including blood, urine, and CSF studies along with hospitalization and use of broad-spectrum antibiotics should be pursued in the febrile infant up to 6 weeks of age. Routine blood tests and blood cultures should not be performed in the 3-month-old to 36-month-old febrile infant unless there are specific indications including, but not limited to, inadequate immunization, constrained family support, or resources. Algorithms that are modified for local application may be pursued in the well-appearing febrile infant aged 6 to 12 weeks.

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