Febrile infant update

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Purpose of review
The approach to febrile young infants remains challenging. This review serves as an update on the care of febrile infants less than 90 days of age with a focus on the changing epidemiology of serious bacterial infection (SBI), refinement of management strategies based on biomarkers, and the development of novel diagnostics.

Recent findings
There is high variability in the emergency department management of febrile young infants without significant differences in outcomes. C-reactive protein (CRP) and procalcitonin have emerged as valuable risk-stratification tests to identify high-risk infants. When interpreting automated urinalyses for suspected urinary tract infection (UTI), urine concentration influences the diagnostic value of pyuria. Novel diagnostics including RNA biosignatures and protein signatures show promise in better identifying young febrile infants at risk of serious infection.

Summary
The majority of febrile infants with an SBI will have a UTI but the diagnosis of invasive bacterial infection in infants continues to be challenging. The use of procalcitonin and CRP as biomarkers in prediction algorithms facilitates identification of low-risk infants.

Keywords
bacteremia, biomarker, fever, meningitis, serious bacterial infection, urinalysis, urinary tract infection

INTRODUCTION

Fever is the most common reason for emergency department (ED) visits by pediatric patients. The febrile young infant has unique clinical considerations given their risk for serious bacterial infection (SBI). Many of these infants appear well and have no localizing signs, yet the morbidity due to invasive bacterial infection (IBI) is substantial, especially when the diagnosis is delayed. Based on this, most EDs follow established protocols for diagnostic evaluation to allow risk stratification; high-risk infants generally receive empiric antibiotics and possibly admission. Given the challenges in identifying young febrile infants with IBI/SBI, additional diagnostic strategies aiding in the identification and risk stratification are being investigated. This review will cover recent updates in the care of febrile infants less than 90 days of age.

BACKGROUND

The diagnosis of SBI in infants is challenging. The incidence of SBI in this population has been estimated at 7–11% [1]. Clinical appearance alone is an insensitive screen for bacterial meningitis and bacteremia, with only 58% of IBI patients identified as clinically ill upon presentation [2]. Numerous low-risk criteria (Philadelphia [3], Boston [4], and Rochester [5]) with negative predictive values (NPVs) ranging from 93.7 to 100% [1] have been established in an attempt to identify those infants who do not require admission for parenteral antibiotics. Complete blood count, urinalysis, blood culture, and urine culture are routine tests in all these strategies. The Boston and Philadelphia criteria include cerebrospinal fluid (CSF) analysis for risk stratification (<60 days of age – Philadelphia, <90 days of age – Boston). In the United States, infants less than 28 days of age are not considered low-risk even if well appearing and without obvious risk factors [6]. The management of well appearing, febrile infants older than 28 days is an area of debate and research.

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KEY POINTS

- The use of procalcitonin and CRP as biomarkers in prediction algorithms facilitates identification of low-risk infants.
- Urine concentration can aid in the interpretation of automated urinalyses to better predict those infants at increased risk of UTI.
- RNA and protein biosignatures show promise in the identification of infants at risk for SBI but are not yet proven.

CHANGING EPIDEMIOLOGY

There has been a shift in the epidemiology of SBI over the preceding 3 decades without a change in the overall SBI rate. Previously, bacteremia represented 20–30% of young infant SBI, with meningitis 0–14% and UTI 30–55% [3,7]. Recent studies have shown a predominance of UTI alone (84%) or in combination with another infection (8.2%), and a corresponding decrease in SBI due to isolated bacteremia (6.3%) and meningitis (0.2%) [8▪]. *Escherichia coli* remains the most common bacterial pathogen detected in blood (60%), urine (87%), and CSF (34%) among infants in a large study of SBI among full-term infants 7–90 days of age. *E. coli* UTI is associated with both bacteremia (bacteremia rate of 13% among infants 7–28 days of age, 8.5% in 29–60 days of age, and 8.9% in 61–90 days) and meningitis (0.3% of infants with *E. coli* UTI) [8▪]. Interestingly, Group B streptococcus (GBS), once the most common cause of bacteremia in neonates, is becoming less prevalent, and Listeria infection is also rare [9▪]. The initiation of guidelines recommending intrapartum antibiotics for colonized women has decreased the prevalence of early-onset GBS without substantially changing that of late-onset GBS [10]. A meta-analysis of the rates of *Listeria monocytogenes* and *Enterococcus* in febrile infants found a prevalence of 0.03 and 0.09% for bacteremia and 0.02 and 0.03% for meningitis, respectively, confirming these organisms as rare causes of IBI in febrile infants [11▪].

As noted above, UTI is the most prevalent SBI among young febrile infants. A large, retrospective study of 670 febrile neonates determined that 15.4% were found to have a UTI. *E. coli* was the pathogen in 71%, including four infants with bacteremia. Interestingly, laboratory parameters were found to be insensitive for diagnosing UTI, with leukocytosis greater than 15 000/μl in only 39% and a positive urine dipstick for leukocyte esterase or nitrite in 79% [12]. In a retrospective review of 132 infants 29–60 days of age discharged home with UTI, 29 subsequently required hospitalization, including five patients with bacteremia. Of the 107 patients discharged for whom outcomes are known, none had adverse events. There remains significant variation (0–20%) among centers in terms of ED disposition for these young infants with fever and a presumptive UTI based on the urinalysis [13].

Although bacteremia is decreasing in prevalence, it remains an important cause of SBI in young infants with fever. Among admitted febrile infants less than 90 days of age, pathogens for bacteremia included *E. coli* (42%), GBS (23%), and *Streptococcus pneumoniae* (6%) [14]. In another large, multicenter review of bacteremia in previously healthy, febrile infants less than 90 days old who were admitted to the hospital, *E. coli* was the predominant pathogen followed by GBS (90% of *E. coli* bacteremia was associated with UTI) [9▪]. In a multicenter, retrospective study on time to blood culture positivity, the mean time to positive blood culture was 15.4 h with 91% of cultures turning positive by 24 h. Interestingly, the youngest infants (less than 30 days old) had a significantly shorter mean time to positivity than did older infants 31–60 and 61–90 days of age (13.9 vs. 15.6 vs. 17.9 h, respectively). *E. coli* (41%) and GBS (22%) accounted for almost two-thirds of the positive cultures in this population [15].

EVOLUTION OF LOW-RISK ALGORITHMS

Even with well established protocols available, there is considerable variation in testing, treatment, and disposition in the management of febrile infants [16▪,17▪]. Using administrative data, Aronson *et al.* [16▪] found considerable variability in ED management of febrile young infants without differences in outcomes. Recognizing that adherence to the recommended management of febrile neonates is variable [16▪,17▪], European investigators developed and validated a new algorithm to more accurately identify a low-risk group who can safely be managed as outpatients without lumbar puncture or empiric antibiotic treatment [18▪▪,19]. In this algorithm (referred to as the Step-by-Step Approach), infants were considered low-risk if they met the following criteria: not ill appearing, age more than 21 days, absence of leukocyturia, procalcitonin (PCT) less than 0.5 ng/ml, C-reactive protein (CRP) less than 20 mg/l, and absolute neutrophil count (ANC) less than 10 000/μl. Although the algorithm performed better in the validation cohort of 2185 febrile infants [18▪▪] than the Rochester criteria or Lab-score [20] [sensitivity 92%, NPV 99.3 vs. 81.6%/98.3% for Rochester criteria, and 59.8%/98.1% for Lab-score],

seven patients with IBI and four with other SBI were missed (compared with 16 infants misclassified by Rochester criteria and 35 by Lab-score). The authors noted that expanding the algorithm to include infants through 28 days would identify an additional four of the seven neonates with IBI but would also reduce specificity [18▪▪]. Although this approach performed better than the more traditional algorithms, the limitations of each algorithm are clear.

ADJUNCTIVE DIAGNOSTIC TESTS

Investigators continue to pursue additional clinical tests to refine risk stratification of young febrile infants. The authors of a single-center retrospective review of febrile neonates propose that CRP is the strongest independent predictor for identifying those at high risk for SBI [as compared with clinical characteristics, ANC, and white blood cell (WBC) count] [21▪]. In Europe, procalcitonin is routinely used in the stratification of young febrile infants. Procalcitonin strongly predicted IBI (OR 21.7 if PCT > 0.5 ng/ml) and performed better than CRP in well appearing, febrile young infants [22]. In a more recent study, PCT was again found to have better diagnostic accuracy than CRP for detecting infants at low risk for IBI (negative likelihood ratio of 0.1 vs. 0.3 for PCT < 0.3 ng/ml and CRP < 20 mg/l, respectively) [23▪]. PCT was also found to be a more accurate biomarker for predicting SBI than WBC, ANC, and absolute band count in a study of febrile children younger than 36 months of age [24▪].

We anticipate an increase in the use of procalcitonin in the United States as it becomes more available. In the meantime, CRP should be considered in risk stratification strategies; at a cut-point of 20 mg/l, febrile infants were 4.9 times more likely to have an SBI (sensitivity 79%, specificity 84%, NPV 97%, and negative likelihood ratio 0.25) [21▪].

In a follow-up study, using the Step-by-Step Approach, the authors investigated outcomes in those low-risk, febrile patients who classified as low-risk and were discharged home without lumbar puncture or antibiotics; only two of 586 patients had definite SBI (occult *Staphylococcus aureus* bacteremia and acute enteritis due to *Salmonella*). Of note, the authors considered infants observed in the ED for up to 24 h as outpatients, with 47% of patients being observed for greater than 12 h prior to being deemed safe for discharge [25▪].

ROLE OF THE LUMBAR PUNCTURE

Whether well appearing, febrile infants require lumbar puncture is a difficult question. In a retrospective review of 1975 well appearing, febrile infants between 21 and 90 days of age, none were diagnosed with bacterial meningitis. Of the 11 (0.46%) patients in the study population ultimately diagnosed with bacterial meningitis, nine were less than 21 days of age and the other two were not well appearing in the ED, leading the authors to suggest that an automatic lumbar puncture is not necessary in well appearing infants greater than 21 days of age [26▪▪]. Using administrative data from 32 US pediatric hospitals, investigators found that centers with guidelines recommending lumbar puncture for febrile infants 29–56 days of age performed more lumbar punctures but a difference in outcome was not observed [27▪].

It is important to recognize that CSF examination in infants with fever is not simply to diagnose bacterial meningitis but also to identify aseptic meningitis or eliminate potential downstream consideration when starting antibiotics for specific focal infections or when administering empiric antibiotics in high-risk infants. Consideration of a lumbar puncture for those with presumed UTI is a special circumstance in which the association between meningitis and UTI is well described [28–30]. Most of the CSF pleocytosis is sterile; however, as noted earlier, bacterial meningitis also occurs especially in febrile neonates. In one large study by Schnadower *et al.* [29] of 1190 febrile infants (29–60 days of age) with UTI, 18% had sterile pleocytosis.

In a single-center retrospective cross-sectional study, low-risk infants between 28 and 60 days with traumatic or unsuccessful lumbar puncture (72.3% of cases) were more frequently hospitalized than those in whom nontraumatic CSF was obtained [31▪]. With this in mind, recent studies have attempted to also increase the success of infant lumbar punctures when indicated. In an attempt to investigate whether dehydration may be a factor associated with decreased success of obtaining CSF in young infants, a novel study of infants with pyloric stenosis attempted to assess changes in sonographic measurement of the subarachnoid space preadministration and postadministration of an intravenous fluid bolus. The study failed to demonstrate any difference after hydration [32▪]. Based on a recent study by Neal *et al.*, the routine use of point-of-care ultrasound (POCUS) should be considered before attempting lumbar puncture in infants. In a prospective, nonblinded, randomized study of 128 infants less than 6 months of age, POCUS-assisted lumbar puncture (marking the site, not dynamic) increased first-attempt success (57.8 vs. 31.3%) and success with three attempts (93.7 vs. 87.5%) [33▪].

FEVER IN YOUNG INFANTS WITH A FOCAL SOURCE OF INFECTION OR CONCOMITANT VIRAL ILLNESS

The specific evaluation of young infants with skin and soft tissue infections (SSTIs) is difficult secondary to limited evidence. Many infants with SSTI are evaluated for additional coexisting IBIs regardless of fever status [34]. A multicenter, retrospective study of 172 infants less than 90 days of age with SSTI found that one patient had bacteremia (0.58%, 95% confidence interval 0.01–3.2%), and there were no cases of bacterial meningitis. The patient with bacteremia was febrile, making the proportion of bacteremia in the febrile group 1 of 25 (4%) vs. 0 of 50 (0%) in the afebrile group [35▪]. Although the data are limited, the authors suggest that afebrile, well appearing young infants with SSTI may be managed without lumbar puncture.

Although a relatively rare disease, neonatal herpes simplex virus (HSV) is associated with high mortality and morbidity. There is widespread variability in HSV testing and empiric acyclovir treatment given the variability in clinical presentation [skin, eye, mucous membrane (SEM), central nervous system (CNS) disease and disseminated HSV (DIS)] and lack of consensus guidelines. A large database review by Aronson *et al.* [16▪] in 2014 found considerable variability in acyclovir utilization between hospitals. Aside from the dilemma of which patients to test and treat for HSV, the best diagnostic approach remains in need of further elucidation. When the diagnosis is being considered, viral culture of mucosal surfaces/suspected lesions is recommended, and PCR of lesions, CSF, and serum can be considered [36]. In a single-center retrospective study of patients with virologically confirmed neonatal HSV (41% SEM, 29% CNS, and 30% DIS), no single diagnostic test (plasma PCR, CSF PCR, and surface culture) was positive for all the infants; however, plasma PCR was the most frequently positive test (83%). Very high plasma HSV PCR levels at presentation were associated with death [37▪]. In an attempt to balance unnecessary acyclovir exposure with the need for expedited diagnosis and treatment in high-risk patients, specific institutions are establishing diagnostic guidelines for testing and empiric acyclovir [36,38▪]. A logical approach, modeled by Cincinnati Children's Hospital, is for all febrile infants younger than 21 days being evaluated for SBI to have CSF HSV PCR testing and if any high-risk features (vesicles, ill appearance, or abnormal CSF parameters) additional tests are considered and empiric acyclovir is administered [38▪].

Logically, febrile infants with identified, viral causes are likely at lower risk of SBI. Byington *et al.* [39] confirmed this in a prospective study of 1779 febrile infants in which the occurrence of SBI was significantly lower in infants with identifiable viral infections (respiratory viruses, enteroviruses, rotavirus, and herpesvirus) compared with those infants without a specific viral infection (4.2 vs. 12.3%).

Although SBI rates are reduced among patients with identified viral infection, the likelihood of SBI also varies by the specific virus. In influenza-positive young infants, 5/218 (2.3%) had associated SBI: four *E. coli* UTIs (one with bacteremia), one case of *Salmonella enteritidis* bacteremia, and no cases of meningitis [40]. In another prospective cohort of 214 febrile infants less than 90 days of age, 20% were enterovirus-positive (PCR from blood and/or CSF); of these infants, 12 infants (5.6%) had concomitant UTI, three (1%) had bacteremia, and no cases of bacterial meningitis were observed [41]. In another prospective cohort study of 90 infants aged 2–12 months with fever and clinical diagnosis of bronchiolitis, concomitant UTI was found in 6.7% [42]. If rapid viral tests are more readily available in the future, this could have implications on the management and treatment of young febrile infants.

DIAGNOSTIC STUDIES FOR URINARY TRACT INFECTION

UTI is the most common cause of SBI in young, febrile infants. Urinalysis is not always an accurate predictor of UTIs in this age group. Urinalysis (positive defined as >5 WBC per high powered field, positive leukocyte esterase or positive nitrite) was positive in only 69% of positive urine cultures in a retrospective review of children aged 2 months through 2 years presenting to the ED with fever [43▪]. In this study, cases of positive urinalysis were associated with a predominance of *E. coli* UTIs, whereas dipstick-negative UTIs were predominantly non-*E. coli*. Adding further to our understanding of interpretation of urinalyses, a recent retrospective study of 2700 infants aged less than 3 months evaluated for UTI illustrated the importance of urine concentration in the interpretation of automated microscopic urinalyses in young infants. Pyuria thresholds of 3 WBC/hpf in dilute urine (specific gravity ≤1.015) and 6 WBC/hpf in concentrated urine (specific gravity greater than 1.015) were optimal in making a presumptive diagnosis of UTI [44▪].

NOVEL DIAGNOSTICS

Given the aforementioned difficulty in identifying those young infants at risk for SBI, studies are

underway to advance our diagnostic repertoire. In a prospective observational study involving 279 randomly selected febrile infants and 19 afebrile healthy controls younger than 60 days of age, RNA biosignatures distinguished those patients with and without bacterial infection (87% sensitivity and 89% specificity) [45▪▪]. Another prospective observational multinational study of 531 children less than 17 years determined a 2-transcript RNA signature that has the potential to discriminate between bacterial and viral infections with sensitivity between 90 and 100% and specificity of 95.8–96% depending on the validation population [46▪▪]. Further studies with larger populations that include young infants are required to further validate the utility of these RNA biosignatures for clinical practice. Another prospective observational study in 1002 adults and pediatric patients (211 children aged less than 3 years), developed a 3 protein signature (tumor necrosis factor-related apoptosis-inducing ligand, IFN-γ-induced protein-10, and CRP) that was superior to any combination of routinely used clinical and laboratory parameters ($\underline{P} < 0.001$) at distinguishing between infectious and noninfectious presentations as well as between bacterial and viral infections [47▪▪]. This protein signature also shows promise; however, further studies are necessary.

CONCLUSION

Although the risk of SBI has not changed over time, UTI has emerged as the most prevalent bacterial infection with bacteremia and bacterial meningitis decreasing in prevalence over time. Low-risk algorithms that incorporate newer biomarkers including procalcitonin and CRP show promise in risk stratification. Incorporating urine concentration in the interpretation of automated urinalyses better helps predict those infants at increased risk of UTI. An identified viral illness decreases an infant's risk of having an SBI. HSV continues to be a diagnostic and management challenge but requires a vigilant approach given its morbidity. RNA and protein biosignatures show promise but are not yet proven.

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Conflicts of interest

There are no conflicts of interest.

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