
Ravi Jhaveri, MD, Carrie L. Byington, MD, Jerome O. Klein, MD, and Eugene D. Shapiro, MD

Although most febrile children aged <3 months have a self-limited viral infection that will resolve without treatment, a small proportion who are not obviously toxic will develop a serious bacterial infection (SBI), including bacteremia, meningitis, and urinary tract infection (UTI). How to best assess and manage such children has long been a matter of debate.1-5 Identifying non–toxic-appearing febrile children with an SBI is a persistent challenge for pediatric practitioners. Management of febrile children is further complicated by the fact that parents and physicians value the risks and costs differently.1 Most physicians find errors of omission (ie, missing a child with SBI) intolerable, and parents give more consideration to procedures involving pain and discomfort for their children, such as diagnostic testing and false-positive test results and their consequences.

History

The risk of SBI is greatest in the immediate neonatal period and during the first months of life, is increased in preterm infants, and decreases progressively with age. Practice has evolved from conservatively managing febrile infants aged <3 months with extensive testing, hospitalization, and treatment with antibiotics to using a combination of clinical appearance, age, and laboratory tests to results to assign the degree of risk of SBI to help guide management.6,7 A meta-analysis from the early 1990s found greater risks of serious bacterial illness, bacteremia, and meningitis in “high-risk” infants versus “low-risk” infants aged <3 months (24.3%, 12.8%, and 3.9% vs 2.6%, 1.3%, and 0.6%, respectively).8 Although a careful evaluation of febrile infants aged <3 months remains important to assess the likelihood of a SBI, clearly many of these infants need not be subjected to rigid algorithms of testing and treatment. Infants aged 61-90 days are at less risk for SBI compared with those aged ≤60 days.9 An observational study of >3000 infants aged <3 months with fever ≥38°C treated by practitioners in 44 states found that the majority (64%) were not hospitalized.10 Practitioners individualized management and relied on clinical judgment; “guidelines” were followed in only 42% of the episodes studied. The infants’ outcomes were excellent. If the guidelines had been followed, outcomes would not have improved, but these infants would have undergone both substantially more laboratory tests and more hospitalizations.1,3,10

Although the risk of SBI is substantially lower in children aged 3 to 36 months, the entity of occult bacteremia (OB; bacteremia in febrile children who on evaluation were thought not to have an SBI and were sent home but a culture of blood obtained at the time grew a potential pathogen) was described in the 1970s.11 Two large studies from the pre–conjugate vaccine era showed that the overall risk of OB in children aged 3 to 36 months age with fever ≥39°C was slightly less than 3%.12,13 Most children with OB had a benign clinical course, but some progressed to severe focal infections. Risk factors for OB included age 6 to 36 months, fever >39.4°C or 103°F, and an elevated white blood cell (WBC) count (>15 000).11,14 The majority of OB cases were caused by Streptococcus pneumoniae (Sp), with a smaller number caused by Haemophilus influenzae type b (Hib) and occasional cases caused by Neisseria meningitidis (Nm), Staphylococcus aureus, Escherichia coli, and Salmonella spp.12,14,15 Based on concerns that children with OB might go on to develop a more serious focal infection, particularly bacterial meningitis, many investigators have attempted to develop strategies for identifying which febrile children are at risk for OB.16 Although some statistically significant associations between test results have been reported (particularly between elevated WBC count and OB), the low prevalence of OB makes the positive predictive value of test results poor (10%-15%).1,17 Moreover, most cases of OB were due to Sp, which often resolved spontaneously.18 Compared with the risk of meningitis in children...

---

CRP C-reactive protein
Hib Haemophilus influenzae type b
HSV Herpes simplex virus
Nm Neisseria meningitidis
OB Occult bacteremia
PCT Procalcitonin
PCV7 Seven-valent conjugate pneumococcal vaccine
SBI Serious bacterial infection
Sp Streptococcus pneumoniae
UTI Urinary tract infection
WBC White blood cell
with occult pneumococcal bacteremia (~1%), the risk of meningitis in children with OB due to Hib and Nm was approximately 12 times and 86 times greater, respectively. In a single trial, Fleisher et al. reported that intramuscular ceftriaxone was effective in preventing meningitis and other bacterial sequelae in young, febrile children at risk for OB. In an attempt to provide a consensus viewpoint, Baraff et al. published guidelines for the diagnosis and management of febrile children at risk for SBI that included routine use of WBC counts to identify children at risk, blood cultures to document the presence of bacteremia, and ceftriaxone therapy for children deemed to be at risk for SBI. These guidelines were considered controversial given the relatively low risk of meningitis (~1/1400), the lack of evidence that either testing for markers of risk or expectant treatment provided substantial benefit to these children, and perceived flaws in study design and analyses that created a bias toward a finding of ceftriaxone’s efficacy in preventing SBI. 

What has Changed Since the 1970s Regarding Management of Febrile Infants without a Focus of Infection?

After introduction of conjugate Hib vaccine in 1988, the incidence of Hib disease in children aged <5 years declined by 99% from 1987-2007. After introduction of the 7-valent conjugate pneumococcal vaccine (PCV7) in 2000, the incidence of pneumococcal meningitis in children aged <2 years fell by 64%, with further decreases anticipated after the introduction of PCV13 in 2010. Chemoprophylaxis during labor to prevent early-onset infection in infants of pregnant women colonized with group B streptococcus also has been effective, with an 80% decrease in early-onset disease documented since publication of the first guidelines in 1996. There has been no concomitant decline in late-onset disease.

In febrile infants aged ≤90 days (the group at greatest risk for SBI), the availability of new diagnostic tests also has improved the accuracy of risk estimation. Abnormalities in total WBC count, absolute neutrophil count, and absolute band count all have been associated with SBI. Total WBC counts <5000/mm³ and >15 000/mm³ have been associated with SBI. Although abnormal WBC counts are not specific for SBI and have a positive predictive value ranging from 26% to 80%, depending on the population being studied, the WBC count, absolute neutrophil count, and absolute band count have SBI, with a likelihood ratio of 2.11 and an area under the receiver operating curve of 0.71. Recent studies continue to document the utility of the WBC count in evaluating febrile infants. In one study of 408 infants aged 7-90 days, those with a WBC count >15 000/mm³ were more likely to have SBI, with a likelihood ratio of 2.11 and an area under the receiver operating curve of 0.71. Another study of 1257 infants found similar results, and also demonstrated that including the complete blood count as part of the evaluation of febrile infants reduced the frequency of missed SBIs.

Elevated C-reactive protein (CRP) and procalcitonin (PCT) levels have been associated with SBI in febrile infants. CRP and PCT tests have superior sensitivity and specificity compared with the WBC count. Because CRP level rises more slowly than PCT level, PCT is a more sensitive test for SBI in infants who have been febrile for <12 hours. Furthermore, CRP level is less specific than PCT level, being elevated in nearly 25% of infants with viral infections. In contrast, PCT is usually normal in infants with viral infections, including respiratory syncytial virus and enteroviral infections, two of the most common causes of fever in infants aged ≤90 days. Although PCT is better than WBC or CRP, the test has some disadvantages, including a longer time until results are available and higher cost. More research is needed to determine whether PCT can be used to identify febrile infants identified as being at high-risk for SBI based on traditional criteria but who actually have a viral illness and can be managed as outpatients and/or without antibiotics.

Viral diagnostic testing also has improved greatly over the last 2 decades. There are now many types of diagnostic tests, including rapid chromatographic immunooassays, direct fluorescent antibody assays, and polymerase chain reaction assays, that are accurate and for which clinical laboratories can often report results in <24 hours. SBIs are less common in febrile infants with laboratory-confirmed influenza, respiratory syncytial virus, and enteroviral infections, The ability to rapidly identify infants with viral infections has resulted in changes in the management of febrile infants aged ≤90 days, as well as older febrile infants and children, including decreased ancillary testing, decreased use of antibiotics, and shorter hospital stays.

What has Not Changed in the Management of Febrile Children without a Focus of Infection?

Modes of pathogenesis that need to be considered include in utero infections, infections acquired at delivery, infections acquired in the nursery, infections acquired in the household, and infections acquired due to underlying anatomic or physiological abnormalities. Many of these problems persist in infants aged 29-90 days, including late-onset group B streptococcus and E coli sepsis. The rate of invasive meningococcal disease is greater during the first year of life greater than at any age; a vaccine has yet to be approved for infants. UTI and urosepsis need be considered in the febrile child without a clinical focus of infection. Selection of children for lumbar puncture remains a challenge for physicians even though the incidence of bacterial meningitis has diminished. Children with an immunosuppressive condition (eg, sickle cell disease, asplenia, human immunodeficiency virus infection, malignancy) are at increased risk for invasive bacterial infections and require aggressive management for febrile episodes.

What are the Issues with Existing Practice Guidelines in the Current Era?

The practice guidelines of Baraff et al. represent an attempt to provide guidance for practitioners faced with the dilemma of managing a febrile child. These guidelines were never officially endorsed by a professional body at the time of initial
publication, but a clinical policy currently endorsed by the American College of Emergency Physicians is virtually identical to the initial recommendations of Baraff et al. These guidelines tout the potential benefits of antibiotic treatment, including prevention of severe sequelae, over the risks of isolating organisms that are contaminants and of performing unnecessary testing. There are several reasons why these guidelines should be modified.

The Guidelines Reflect Epidemiology from 25 Years Ago, Not from Today
Even before introduction of the Hib conjugate vaccine, Hib was the causative organism in only a minority of children with OB who presented with fever without localizing signs, although it was the most common organism associated with serious focal infections. With the universal administration of Hib vaccine to infants starting in the late 1980s, Hib disease has virtually disappeared, as has many of the serious sequelae of OB that the original guidelines were designed to prevent.

The Guidelines Treat All Agents That Cause Bacteremia Equally in Terms of Subsequent Risks When This is Not Accurate
After elimination of Hib, the occurrence of complications of OB due to Sp was the major justification for continued testing and empiric treatment of these febrile children. Although Sp was the most common cause of OB, it was not associated with the same risk of severe complications. The vast majority of cases of OB due to Sp resolved either without treatment or with oral antibiotic therapy.

In 2000, with the approval of PCV7 pending, investigators calculated that routine use of PCV7 would eliminate 97% of OB cases due to Sp. Several subsequent studies have proven this prediction, with reported Sp OB rates of <0.5% (Table). Studies also have shown that contaminants are isolated from blood cultures 10 to 20 times more often than pathogens, and that WBC counts are no longer a useful way to evaluate the risk of OB in children aged >90 days. Although surveillance data demonstrate that nonvaccine serotypes are the major cause of invasive pneumococcal disease today, overall rates of invasive pneumococcal disease remain stable at levels ~50% lower than before the introduction of PCV7. Nonvaccine serotypes cause predominantly sinopulmonary infections, including empyema and sepsis, associated with “obvious” rather than occult bacteremia.

Nm can cause OB leading to serious complications. However, Nm is far less common than Sp, and current rates of invasive disease are >60% lower than those observed in the 1990s, so Nm is a rare cause of SBI in children with OB. Universal immunization of adolescents may further decrease the reservoir and protect young children who are not currently targeted for immunization.

The Guidelines do Not Sufficiently Focus on UTI, the Most Common SBI in Febrile Children
Many studies have shown that the most common SBI in children with fever without localizing signs is UTI, which occurs in 4%-6% of febrile children and in up to 8.2% of febrile infants classified as high risk (3.4% in viral-positive vs 10.4% in viral-negative infants). Studies have shown that girls are at greater risk than boys, with the sex differential increasing significantly with age. Although current recommendations, including those of the American Academy of Pediatrics, include evaluation of urine, studies have shown that this is not always done. New guidelines should emphasize evaluation for UTI in all febrile infants and young children without localizing signs, with the possible exception of circumcised boys.

In an Era of Increasingly Limited Resources, Guidelines Should be Demonstrated to be Cost-Effective
In the current health care environment, the costs and benefits of every evaluation and intervention must be assessed. In 2001, an assessment of various strategies for evaluation of febrile infants without localizing signs found that for rates of OB at or below our current rate of 0.5%, no screening and/or preemptive treatment strategies were cost-effective compared with clinical assessment. A cost-benefit has been demonstrated for diagnosis of UTI in children, taking into account the long-term risk of renal scarring and overall diminished quality of life.

A discussion of febrile infants would not be complete without a mention of herpes simplex virus (HSV) infection in early infancy. Many cases of HSV present with focal signs (skin lesions, seizures) that provide an obvious direction for evaluation and management; however, approximately one-third of infants with HSV infection present with fever.

### Table. Rates of OB after the introduction of PCV7

<table>
<thead>
<tr>
<th>Reference</th>
<th>Site, years, number of children</th>
<th>Pathogens</th>
<th>Contaminants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoll and Rubin</td>
<td>Long Island, 2001-2003; 329 children</td>
<td>0.9% Sp (3 episodes in 2 patients; 1 unvaccinated)</td>
<td>1.2%</td>
</tr>
<tr>
<td>Carstairs et al</td>
<td>San Diego, 2000-2002; 1383 children</td>
<td>0% after PCV7; 2.4% with no PCV7 (1% of overall)</td>
<td>3%</td>
</tr>
<tr>
<td>Sard et al</td>
<td>Boston, 1997-2005; 2971 children</td>
<td>0.7% overall (0.45% Sp)</td>
<td>2.8%</td>
</tr>
<tr>
<td>Waddle and Jhaveri</td>
<td>Durham, 1997-1999; 2001-2004; 423 children</td>
<td>6.7% pre-PCV7; 0.4% post-PCV7; 4% vs 0% Sp</td>
<td>4.7%</td>
</tr>
<tr>
<td>Wilkinson et al</td>
<td>Phoenix, 2004-2007; 8408 children</td>
<td>0.25% Sp</td>
<td>1.89%</td>
</tr>
</tbody>
</table>
lethargy, or poor feeding.47,48 The possibility of HSV infection should be considered in neonates with unexplained fever, particularly during the first month of life. Infants with disseminated HSV are the most likely to have nonspecific signs of illness and the least likely to be evaluated and treated for HSV, and have the highest mortality. The diagnosis should be pursued if there are signs that suggest HSV, such as skin lesions or seizures, and should be considered in infants with nonspecific laboratory findings, including elevated hepatic enzymes or mononuclear cerebrospinal fluid pleocytosis with negative test results for bacteria and enteroviruses, or in infants presenting during a season when enteroviruses are not prevalent (winter or spring).47

What Should the New Guidelines Include?

It is important to emphasize that regardless of age, an infant or child deemed to be seriously ill- or toxic-appearing requires complete evaluation and, in most cases, antimicrobial therapy. For infants aged ≤30 days, a full evaluation of blood, urine, and cerebrospinal fluid for those considered high risk by Rochester or similar criteria is still favored in most circumstances, with infants aged 31-90 days considered at intermediate risk for SBI, for whom acceptable management can range from a complete evaluation to simply observation and follow up. Infants with laboratory-documented viral illness may not require as extensive an evaluation. For infants and children aged 3 to 36 months, an evaluation of urine is warranted. For those who have received at least 2 doses of both Hib and pneumococcal conjugate vaccines, additional testing beyond urine evaluation is no longer necessary. Children who are unimmunized or underimmunized still may be protected if they are surrounded by children who are fully immunized. This more limited approach has long been advocated by many experts.49,50 Although the United States has not had any new content guidelines/policies since 1993, the United Kingdom, which started using PCV7 in 2006, has developed new policies for evaluation of infants and children with fever.51 The UK guidelines recommend clinical assessment for toxicity, routine evaluation of the urine, and elimination of routine use of blood counts, blood cultures, and antibiotic therapy in non–toxic-appearing children aged 3 months to 3 years. In the United States, these policy and practice changes are long overdue.

Summary

Although controversy remains as how to best manage acutely febrile infants and children, there are several areas of near consensus. Infants aged ≥60 days continue to have the highest rates of SBI and pose a challenge to practitioners attempting to determine how extensive an evaluation to perform in a non–toxic-appearing child. UTIs are the most common SBIs in all age groups. It is our opinion that assessment for UTI should be part of any evaluation for all but the lowest-risk patients (ie, circumcised boys). New technologies to can more rapidly diagnose common viral and bacterial infections and recommendations to simplify the management of these febrile infants and children are needed. ■

Submitted for publication Dec 3, 2010; last revision received Feb 17, 2011; accepted Mar 22, 2011.

Reprint requests: Ravi Jhaveri, MD, Duke University Medical Center, Division of Pediatric Infectious Diseases, Box 3499, Durham, NC 27710. E-mail: ravi.jhaveri@duke.edu

References


