Management of the Non–Toxic-Appearing Acutely Febrile Child: A 21st Century Approach

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Although most febrile children aged <36 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 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.[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 influenza* type b (Hib) and occasional cases caused by *Neisseria meningitidis* (Nm), *Staphylococcus aureus*, group A streptococcus, *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%).[2,17] 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 influenza* 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

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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.[19] In a single trial, Fleisher et al[12] 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[15] 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.[2,12,20]

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.[20-22] 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.[23] 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/mm^3 and >15 000/mm^3 have been associated with SBI.[8] 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 cutoff value used, and how SBI is defined,[6,24] 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/mm^3 were more likely to have SBI, with a likelihood ratio of 2.11 and an area under the receiver operating curve of 0.71.[25] 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.[26]

Elevated C-reactive protein (CRP) and procalcitonin (PCT) levels have been associated with SBI in febrile infants.[25] CRP and PCT tests have superior sensitivity and specificity compared with the WBC count.[24,25] 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.[24,25] Furthermore, CRP level is less specific than PCT level, being elevated in nearly 25% of infants with viral infections.[24] In contrast, PCT is usually normal in infants with viral infections, including respiratory syncytial virus and enteroviral infections,[24,27] two of the most common causes of fever in infants aged ≤90 days.[28] 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 immunoassays, 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.[28-32] 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.[33,34]

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[15] 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