14 Fever without Localizing Signs

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The vast majority of young children with fever and no apparent focus of infection have self-limited viral infections that resolve without treatment and are not associated with significant sequelae. However, a small proportion of them who do not appear to be seriously ill may be in the early stages of a serious bacterial infection or may have occult bacteremia. A very small proportion of the latter group may subsequently develop a serious focal infection such as meningitis. Despite numerous studies that attempted both to identify the febrile child who appears well but who actually has a serious infection and to assess effectiveness of potential interventions, no clear answers have emerged.[1–4] Studies show that parents generally are more willing than are physicians to assume the small risk of serious adverse outcomes in exchange for avoiding the short-term adverse effects of invasive diagnostic tests and antimicrobial treatment.[5,6] The best approach to the management of the febrile child combines informed estimates of risks, careful clinical evaluation and follow-up of the child, and judicious use of diagnostic tests.[7]

TABLE 14-1. Age-Related Causes of Serious Bacterial Infections in Very Young Infants

BACTEREMIA/MENINGITIS	
<1 month	*Escherichia coli* (and other enteric gram-negative bacilli)
	Group B streptococcus
	Listeria monocytogenes
	Streptococcus pneumoniae
	Haemophilus influenzae
	Staphylococcus aureus
	Neisseria meningitidis
	Salmonella spp.
1–3 months	*Streptococcus pneumoniae*
	Group B streptococcus
	Neisseria meningitidis
	Salmonella spp.
	Haemophilus influenzae
	Listeria monocytogenes
OSTEOARTICULAR INFECTIONS	
<1 month	Group B streptococcus
	Staphylococcus aureus
1–3 months	*Staphylococcus aureus*
	Group B streptococcus
	Streptococcus pneumoniae
URINARY TRACT INFECTION	
0–3 months	*Escherichia coli*
	Other enteric gram-negative bacilli
	Group D streptococcus (including *Enterococcus* species)

ETIOLOGIC AGENTS

The list of microbes that cause fever in children is extensive. Relative importance of specific agents varies with age, season, and associated symptoms. The focus of this chapter is the febrile child with occult bacterial infection.

Table 14-1 shows the most common causes of serious bacterial infection in children younger than 3 months.[8,9] The division at 1 month is not absolute; considerable overlap exists. Also, certain viruses, notably herpes simplex and enteroviruses, can cause serious infections in neonates, mimicking septicemia.

In children 3–35 months of age, most bacterial infections with no apparent focus are caused by *Streptococcus pneumoniae* (in unimmunized children), *Neisseria meningitidis,* or *Salmonella* spp. (the latter often occurring in association with symptoms of gastroenteritis). *Haemophilus influenzae* type b has become rare and incidence of *Streptococcus pneumoniae* infection has fallen substantially since universal administration of effective vaccines began.[10,11] Other common causes of invasive bacterial infections, such as *Staphylococcus aureus,* are usually associated with identifiable foci of infection.

EPIDEMIOLOGY

Children Younger than 3 Months

Risk of serious bacterial infection varies with age. Although longitudinal studies indicate that during their first 3 months only 1% to 2% of children come to medical attention for fever, a greater proportion of such febrile infants have serious bacterial infections than do older children.[12–15] Risk is greatest during the immediate neonatal period and through the first month (and is heightened in the infant born prematurely).

In a prospective study, researchers in Rochester identified factors associated with a low risk of serious bacterial infection in febrile infants younger than 3 months.[16] Among 233 infants who were born at term with no perinatal complications or underlying diseases, who had not received antibiotics, and who were hospitalized for fever, 144 (62%) were considered unlikely to have a serious bacterial infection and fulfilled all of the following criteria: (1) no clinical evidence of infection of the ear, skin, bones, or joints; (2) white blood cell (WBC) count between 5000 and 15,000/mm^3; (3) <1500 band cells/mm^3; and (4) normal results

of urinalysis. Only 1 of these 144 infants (0.7%) had a "serious" bacterial infection (*Salmonella* gastroenteritis), and none had bacteremia. By contrast, among the 89 infants who did not meet these criteria, 22 (25%) had a serious bacterial infection ($P<0.0001$) and 9 (10%) had bacteremia ($P<0.0005$).

Subsequent investigations largely have corroborated results of the Rochester study.[17–20] Although investigators have used slightly different criteria to define young febrile infants at low risk of serious bacterial infection, all found that the risk of a serious bacterial illness in the group defined as being at low risk is, indeed, very low. In a meta-analysis of studies of febrile children younger than 3 months, the risks of "serious bacterial illness," bacteremia, and meningitis were 24.3%, 12.8%, and 3.9%, respectively, in "high-risk" infants and 2.6%, 1.3%, and 0.6%, respectively, in "low-risk" infants.[15] The negative predictive value for serious bacterial illnesses of infants fulfilling low-risk criteria ranged from 95% to 99% (and was 99% for bacteremia and 99.5% for meningitis).[15] Thus, clinical and laboratory assessment can be used to identify the slightly more than 50% of febrile infants <3 months of age at very low risk of serious bacterial infections.

An observational study of more than 3000 infants <3 months of age with fever >38°C treated by practitioners and reported as part of the Pediatric Research in Office Settings network found that the majority (64%) were not hospitalized.[3,21] Practitioners individualized management and relied on clinical judgment; "guidelines" were followed in only 42% of episodes.[3,21,22] Outcomes of the children were excellent. If the guidelines had been followed, outcomes would not have improved but there would have been both substantially more laboratory tests performed and more hospitalizations.[3]

Risk of serious bacterial infection has fallen further with the marked reduction in early-onset group B streptococcal infections because of effective peripartum antimicrobial prophylaxis of colonized pregnant women.[23] Risk of serious bacterial infections also is lower in febrile children who have an identified viral infection.[24]

Children 3 Months and Older

During the 1970s, reports of occult pneumococcal bacteremia began to appear.[25] Some children aged 3 months or older with fever who did not appear to be toxic and who had no apparent focus of infection had bacteremia, most often due to *Streptococcus pneumoniae* but occasionally due to *H. influenzae* type b or *N. meningitidis.*[25–32] Moreover, in some instances, serious focal infections such as meningitis developed in children with occult bacteremia.

The overall rates of bacteremia reported in studies of these febrile children range from 3% to 8%.[33] Fever alone is not associated with an excessive risk of bacteremia; the two largest studies of children 3 to 36 months of age with fever ≥39°C and no apparent focus of infection documented bacteremia in 2.8% (27 of 955) and 2.9% (195 of 6733) of children, respectively.[34,35] Frequency of occult bacteremia in disadvantaged urban populations and in suburban populations served by private practitioners is similar.[36,37] Risk of bacteremia is greater when very high fever is associated with high total WBC count.[22,27,33,38,39]

Most children with occult bacteremia have transient infection and recover (even without antimicrobial therapy) without having a serious complication such as meningitis or septic shock.[22,40–46] Risk of meningitis complicating occult bacteremia varies with bacterial species. Compared with the risk of developing meningitis with occult pneumococcal bacteremia (4 of 225; 1.8%), the odds of developing meningitis was 15 times greater for children with occult *H. influenzae* type b bacteremia and 81 times greater for children with occult *N. meningitidis* bacteremia.[32]

Risk of meningitis among children with occult bacteremia decreased substantially when occult bacteremia due to *H. influenzae* type b was virtually eliminated with introduction of the conjugate vaccine;[10,47] among children aged 3 to 35 months who are evaluated for high fever without a focus, it was estimated that bacterial meningitis would develop subsequently in approximately 1 of 1000 to 1500 untreated children.[6] Consequently, even if "expectant" antimicrobial treatment of febrile children were 100% effective, it would have been necessary to treat 1000 to 1500 children to prevent 1 case of meningitis. In the United States, after introduction in 2000 of the polysaccharide–protein conjugate vaccine against 7 serotypes of pneumococci, substantial reduction in incidence of invasive disease has been documented in vaccinated children.[7,11] However, during this time there was a small increase in pneumococcal infections caused by serotypes not included in the vaccine, many of which, while less likely to be associated with bacteremia and meningitis than were some of the types in the vaccine, were still able to cause serious infections such as pneumonia and empyema.[7] In 2010, replacement of the 7-valent vaccine with a 13-valent conjugate pneumococcal vaccine promises to lead to additional decreases in serious bacterial infections in children caused by pneumococci and to further reduction of occult bacteremia and its consequences.[48]

LABORATORY FINDINGS AND DIAGNOSIS

Various diagnostic tests to quantify the risk of bacteremia and its complications have been assessed including the WBC count and differential, microscopic examination of buffy coat of blood, erythrocyte sedimentation rate, C-reactive protein, procalcitonin serum levels, morphologic changes in peripheral blood neutrophils, and quantitative cultures of blood.[22,38,49–55] In addition, clinical scales have been developed to help identify the febrile child with a serious illness.[56]

Unfortunately, no test has sufficient sensitivity and positive or negative predictive value to be clinically useful for an individual patient. In one prospective study of children with a temperature >40°C, those with a WBC count of ≥15,000/mm^3 had three times greater risk of bacteremia than did those with a WBC count of <15,000/mm^3.[27] However, the positive predictive value of this test for bacteremia was only 14%; thus, more than 85% of highly febrile children with a WBC count of ≥15,000/mm^3 did not have bacteremia. Others have reported similar results.[38,57] Subsequent to these studies, the prevalence of occult bacteremia diminished markedly because of introduction of vaccines effective against common causes of occult bacteremia and serious bacterial infections, so the positive predictive value of such test results is now substantially lower. Consequently, such testing as a routine can no longer be justified.[4,7,58]

The outcome of primary concern is not occult bacteremia but meningitis. An ideal diagnostic test would specifically identify febrile children at risk of a serious complication, because many focal infections after bacteremia (e.g., most cases of either pneumonia or cellulitis) can be treated when they become apparent and are not usually associated with serious sequelae. Unfortunately, there is no such test. Lowering the risk of serious complications by preventing infections through use of conjugate vaccines has proven to be the most effective strategy.

MANAGEMENT

Although there is no single correct approach to the management of febrile infants without localizing signs who appear well, studies have provided data upon which informed decisions can be based.[7] There is general agreement that febrile children who are "very young" (variably considered to be younger than 3, 2, or 1 month of age) should be managed differently from the way in which older children are managed.

Children Younger than 3 Months

Because of the substantially greater risk of serious infections in very young infants with fever and the difficulty in assessing degree of wellness accurately, pediatricians have approached the management of such infants conservatively. Some clinicians adhere to a protocol of treating all young infants with fever and no apparent focus of infection with broad-spectrum antimicrobial agents administered intravenously in the hospital until the results of

cultures of the blood, urine, and cerebrospinal fluid (CSF) are known.[59] Although sometimes perceived as the "safe" approach, such management incurs considerable financial cost and risk of iatrogenic complications and of diagnostic misadventures associated with hospitalization.[60–62] These risks include errors in the type and dosage of drugs, complications of venous cannulation (such as phlebitis and sloughing of the skin), and nosocomial infections. In addition, hospitalization of a young infant is a major disruption for the family and may potentiate the development of the "vulnerable child" syndrome.[63]

Investigators have found that selected young infants with fever can do well without hospitalization.[3,7,17,18,21,64] Consequently, many experts believe that febrile infants from 2 to 3 months of age with no apparent focus of infection who appear well and/or who have a laboratory-documented viral infection can be managed without either additional laboratory tests or hospitalization, provided that careful follow-up is ensured.[7] Others require laboratory criteria predictive of low risk (some include normal CSF analysis in the criteria). Some would simply observe the patient very closely without giving antimicrobial therapy; others would treat all such infants for 2 days with a single daily dose of ceftriaxone while awaiting the results of the cultures. Either approach can be defended.

If an antimicrobial agent is to be administered, cultures of the blood, urine, and CSF should be obtained first. Rapid tests for specific viral pathogens, which now are widely available, may aid decisions about managing patients and may reduce the need for and/or the duration of hospitalization.[7,65] Febrile infants at low risk of serious bacterial infection for whom adequate home observation and follow-up cannot be ensured should be hospitalized and can be observed without antimicrobial treatment. Doing so (if the child appears well) is reasonable and avoids the adverse side effects of antimicrobial agents and intravenous cannulation, shortens the duration of hospitalization, and saves money without placing the child at significant risk of complications.[18,21,64]

Most febrile infants with no apparent focus of infection who are younger than 1 month should be hospitalized and treated with antimicrobial therapy, although, in selected instances, hospitalization without antimicrobial treatment, or management as an outpatient (after laboratory evaluations, including analysis of CSF), may be reasonable. If a decision is made to administer antimicrobial agents intravenously, ampicillin plus gentamicin provides a suitable spectrum of activity until results of cultures permit discontinuation or alteration of treatment. Ampicillin plus a third-generation cephalosporin such as cefotaxime could be chosen, but there is no proven benefit in children without meningitis. Before initiating antimicrobial treatment, cultures of the blood, urine (obtained by either urethral catheterization or suprapubic aspiration of the bladder), and CSF should be obtained.

Children Older than 3 Months

Children older than 3 months of age who appear well and have no apparent focus of infection can be followed clinically without laboratory tests or treatment with antimicrobial agents; risk of occult or of serious bacterial infection is extremely low. For febrile children (i.e., those with a temperature ≥39°C) aged 3 to 35 months, there has been controversy about whether and which diagnostic tests should be performed and whether "expectant" antimicrobial treatment should be initiated.[6,7,22] Although results of a complete WBC count and differential may help to identify children at increased risk of occult bacterial infection, these tests have no direct therapeutic impact, and their positive predictive value is poor. Substantial evidence suggests that obtaining blood cultures routinely in these children has little impact on outcome (although false-positive blood culture results lead to substantial unnecessary costs).[66,67] The authors of a carefully conducted decision analysis concluded that a strategy of obtaining blood cultures in all such febrile children did more harm than good, in part because many children in whom bacteremia spontaneously clears are hospitalized and treated unnecessarily.[1] With the further decrease in the frequency of occult bacteremia and its complications since introduction of conjugate pneumococcal vaccine, the balance is shifting even further away from benefit for routine testing of these children.[7] Indeed, isolates from cultures of the blood of are now substantially more likely to be contaminants than to be pathogens.[7]

Furthermore, it is not clear that "expectant" therapy of febrile children prevents serious complications such as meningitis. Two large randomized clinical trials were conducted of the efficacy of "expectant" antimicrobial treatment in preventing focal complications in all febrile (temperature of ≥39°C) children 3 to 36 months of age with no apparent focus of infection.

In the first trial, 955 children were randomized to receive either amoxicillin or placebo in a double-blind manner; no statistically significant difference in outcomes was observed.[34] However, because of the rarity of focal complications of bacteremia, 2 of 10 (10%) patients in the amoxicillin group and 1 of 8 (12.5%) patients in the placebo group, there was insufficient statistical power to exclude the possibility that amoxicillin is effective.

In the other clinical trial, 6733 children aged 3 to 36 months with a temperature of ≥39°C and no apparent focus of infection (or with otitis media) were randomized to receive 1 dose of ceftriaxone (50 mg/kg) or amoxicillin (20 mg/kg per dose) three times a day for 2 days.[35] Among children with occult bacteremia, no statistically significant difference was observed in the frequency of definite and probable complications (ceftriaxone, 3 of 101 (3.0%) patients; amoxicillin, 6 of 91 (6.6%) patients). Although the investigators seemed to endorse routine use of ceftriaxone, their methods and conclusions have been criticized.[6,68] Criticisms have included biased definition of the outcomes (a positive culture at follow-up is less likely in patients treated with ceftriaxone if focal infection was incipient or already present at enrollment), incomplete follow-up, and inappropriate statistical analyses. Furthermore, 4 of 5 children in whom meningitis developed were infected with *H. influenzae* type b, a disease that now has been virtually eliminated. Consequently, even if one accepted the investigators' conclusions, these data no longer apply.

Routine antimicrobial treatment of febrile children for possible occult bacteremia is not without risk.[6,7,69] In addition to substantial financial costs, antimicrobial agents have predictable as well as idiopathic adverse side effects. Widespread use of antibiotics selects for resistant organisms. In addition, loss of clinical improvement as a marker of natural history of infection in a partially treated child, difficulty in interpreting mildly abnormal CSF at follow-up, and frequent contaminated blood cultures all lead to increased frequency of unnecessary hospitalization and increased use of laboratory tests and of antimicrobial therapy. Perhaps most important, thoughtful assessment, individualized management, and close follow-up of the febrile child may be forgotten.

In view of current data, including the marked reduction in the incidence of invasive infections with vaccine-preventable pathogens in children, the following approach seems appropriate: The febrile child should be carefully assessed for foci of infection and, if found, should be treated according to likely pathogens. If the child appears toxic, appropriate cultures and diagnostic tests should be performed and antimicrobial treatment, usually with ceftriaxone, should be initiated (some would add vancomycin); most such children should be hospitalized. If no focus is found and the child does not appear toxic, no diagnostic tests are indicated routinely. Parents should be instructed to look for signs that a more serious problem is developing (e.g., persistent irritability or lethargy, inattentiveness to the environment). Serial observations should be planned that will permit subsequent clinical and laboratory evaluation and antimicrobial treatment as indicated.

Other Considerations

This chapter focuses on invasive bacterial infections (particularly bacteremia) as a cause of fever without apparent focus. It should not be forgotten that urinary tract infection is an important cause of fever in young children.[70] Indeed, urinalysis may be a more appropriate diagnostic test in the febrile infant than complete

blood count or blood culture.[6,7,71] In addition, viral infections are the major cause of fever in infants and toddlers. Human herpesvirus 6 (and, to a lesser extent, human herpesvirus 7), influenza, respiratory syncytial virus, rhinovirus, and enteroviruses have been implicated as common causes of fever in young children.[7,72–74] Although other serious illnesses, such as autoimmune diseases and inflammatory bowel disease, can manifest as fever without a focus, they are rare and come to attention because of persistence or recurrence of fever (see Chapter 15, Prolonged, Recurrent, and Periodic Fever Syndromes).

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