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14 Fever Without Localizing Signs

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Most 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 young children with fever who do not appear to be seriously ill may be seen early in the course of a bacterial infection that could progress to bacteremia or meningitis. Despite numerous studies that have attempted to identify the febrile child who appears well but has a serious infection and to assess the effectiveness of potential interventions, no clear answers have emerged.[1–4] Studies show that parents usually are more willing than 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 treatment 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]

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 goal of this chapter is to assist in identifying the febrile child with a serious bacterial infection (SBI).

Table 14.1 shows the most common causes of SBI in children younger than 3 months.[8–12] The division at 1 month is not absolute; considerable overlap exists. Receipt of vaccines typically administered at 2 months also reduces the risk of SBI. Certain viruses, notably herpes simplex, influenza, and enteroviruses, can cause serious infections in neonates, mimicking septicemia and beginning as fever with no apparent focus of infection. Less serious viral infections are the most common causes of fever in children of all ages.

In children between 3 and 35 months of age, most bacterial infections with no apparent focus are caused by *Streptococcus pneumoniae* (in unimmunized children), *Neisseria meningitidis,* or *Salmonella* spp. infection (which often is associated with symptoms of gastroenteritis). Because universal administration of pneumococcal and *Haemophilus influenzae* type b (Hib) conjugate vaccines, Hib has become rare, and the incidence of infection with *S. pneumoniae* has fallen substantially.[13,14] Other common causes of invasive bacterial infections in these children, such as *Staphylococcus aureus,* are usually associated with identifiable focal infections.

EPIDEMIOLOGY

Children Younger Than 3 Months

The risk of serious bacterial infection varies with age. Although longitudinal studies have shown that only 1% to 2% of children are brought to medical attention for fever during the first 3 months of life, a greater proportion of febrile infants has serious bacterial infections than older children.[15–18] Risk is greatest during the immediate neonatal period and through the first month of life, and risk is heightened for infants born prematurely.

In a prospective study conducted by investigators at the University of Rochester, factors were identified that indicate a low risk of serious bacterial infection in febrile infants younger than 3 months.[19] 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 and possible septicemia, 144 (62%) were considered unlikely to have a serious bacterial infection and fulfilled all of the following criteria: no clinical evidence of infection of the ear, skin, bones, or joints; white blood cell (WBC) count between 5000 and 15,000/mm^3; less than 1500 band cells/mm^3; and normal urinalysis results. Only 1 (0.7%) of the 144 infants had a serious bacterial infection (i.e., *Salmonella* gastroenteritis), and none had bacteremia. In 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 ($P < 0.0005$).

TABLE 14.1 Age-Related Causes of Serious Bacterial Infections in Very Young Infants

Age Group	Causative Bacteria
BACTEREMIA OR MENINGITIS	
<1 month	*Escherichia coli* Other enteric gram-negative bacilli Group B *Streptococcus* *Streptococcus pneumoniae* *Staphylococcus aureus* *Salmonella* spp. *Neisseria meningitides* *Streptococcus pneumoniae* *Listeria monocytogenes*
1–3 months	*Escherichia coli* Other enteric gram-negative bacilli Group B *Streptococcus* *Salmonella* spp. *Neisseria meningitides*
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 *Enterococcus* species

Many studies have largely corroborated results of the Rochester study.[11,12,20–25] Although investigators have used slightly different criteria to define young febrile infants at low risk for serious bacterial infection (and some investigators excluded children younger than 1 month old), all found that the risk of a serious bacterial illness in the group defined as being at low risk is very low. Approximately 10% of young febrile infants have urinary tract infections (UTIs), largely due to *Escherichia coli*, and 10% of this group (1% overall) have concomitant bacteremia or meningitis.[11,12,26]

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, for high-risk infants and 2.6%, 1.3%, and 0.6%, respectively, for low-risk infants.[15] The negative predictive value (NPV) for serious bacterial illnesses among infants fulfilling low-risk criteria ranged from 95% to 99%, and the NPV was 99% for bacteremia and 99.5% for meningitis.[15] Although the risk of serious bacterial infection is high among febrile infants younger than 3 months of age with no apparent focus of infection, clinical and laboratory assessment can identify the slightly more than 50% of infants at very low risk.

An observational study of more than 3000 infants younger than 3 months of age with fever greater than 38°C treated by practitioners and reported as part of the Pediatric Research in Office Settings Network found that 64% were not hospitalized.[4,27] Practitioners individualized management and relied on clinical judgment; guidelines were followed in only 42% of episodes.[4,27,28] Outcomes of the children were excellent. If the guidelines had been followed, outcomes would not have improved, but there would have been substantially more laboratory tests performed and more hospitalizations.[4]

Risk of serious bacterial illness in young infants has fallen further due to the marked reduction in early-onset group B streptococcal infections because of the effectiveness of peripartum antimicrobial prophylaxis of pregnant women with positive screening test results for colonization with group B *Streptococcus*.[29] In febrile children younger than 3 months of age who have an identified viral infection such as influenza, respiratory syncytial virus (RSV), or enteroviruses, the risk of a serious bacterial infection other than a UTI falls to almost zero.[24,30–33]

Children Older Than 3 Months

In the 1970s and 1980s, there was concern about occult bacteremia in febrile children between 3 months and 24 to 36 months of age.[34] Studies performed in that era showed that some children 3 months of age 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 *S. pneumoniae* but occasionally due to Hib or *N. meningitidis*.[34–41] In some instances, serious focal infections such as meningitis developed in children with occult bacteremia.

The concern about progression to focal infections resulted in protocols being developed to identify and intervene for infants at high risk. Protocols emphasized routine blood cultures and empiric antibiotic administration for many febrile children in this age group.[28] These practices discounted several facts. First, most children with occult bacteremia have transient infection and recover without antimicrobial therapy and without developing a serious complication (e.g., meningitis, septic shock).[28,42,43] Second, risk of meningitis complicating occult bacteremia varies with bacterial species (*N. meningitidis* ≫ Hib ⋙ *S. pneumoniae*).[35] Third, universal vaccination against Hib led to elimination in vaccinated infants of the most concerning occult bacteremia, and subsequent use of conjugate pneumococcal vaccine eliminated almost all other cases of occult bacteremia.[44–49]

The risk of UTI in well-appearing febrile children in this age group has not changed significantly over the years. Several studies have shown that the rate of UTI varies among different populations (e.g., girls vs. boys, uncircumcised vs. circumcised) within this age group and varies with height and duration of fever. UTI should be considered as a potential source of SBI in these patients.[44,50]

LABORATORY FINDINGS AND DIAGNOSIS

Various diagnostic tests to quantify the risk of bacteremia and its complications have been assessed. They include the WBC count and differential count, microscopic examination of buffy coat of blood, erythrocyte sedimentation rate, C-reactive protein, procalcitonin, morphologic changes in peripheral blood neutrophils, and quantitative cultures of blood.[28,51–58] Clinical scales have been developed to help identify the febrile child with a serious illness.[59]

Unfortunately, no test has sufficient sensitivity and positive predictive value (PPV) or NPV to be clinically useful for an individual patient. In the era before conjugate vaccinations for Hib and *S. pneumoniae,* several studies examined the risk of bacteremia among children with a temperature higher than 40°C and in those with fever and a WBC count of at least 15,000/mm.[3,41,51,60] The PPV of the tests for bacteremia was only about 15%. In the current era of low incidence and unconfirmed predictive value of WBC for remaining pathogens, laboratory testing no longer is justified.[1,7,45,47]

Making a laboratory-confirmed diagnosis of a viral infection significantly reduces the likelihood that a febrile infant has a concomitant bacterial infection (with the exception of a UTI). This currently holds true for influenza, RSV, and enterovirus, and in the future, it will likely be true for many other respiratory viruses (e.g., human metapneumovirus, parainfluenza virus, coronavirus) that are being diagnosed with multiplex polymerase chain reaction (PCR) technology. One study showed that incorporating viral diagnostics into the initial evaluation of febrile infants reduced the length of hospitalization and healthcare costs.[61]

MANAGEMENT

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

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 the degree of wellness accurately, pediatricians have approached the management of these cases 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.[62] Although perceived as the safe approach, it incurs considerable financial cost and risk of iatrogenic complications and of diagnostic misadventures associated with hospitalization.[63–65] These risks include errors in the type and dosage of drugs, complications of venous cannulation (e.g., phlebitis, sloughing of the skin), and nosocomial infections. Hospitalization of a young infant is a major disruption for the family and may potentiate development of the vulnerable child syndrome.[66]

Investigators have found that selected young infants with fever can be treated expectantly without hospitalization.[4,7,19,21,27,67] Consequently, many experts think that febrile infants between 4 and 12 weeks of age with no apparent focus of infection who appear well or have a laboratory-documented viral infection can be treated without additional laboratory tests or hospitalization, provided that careful follow-up is ensured.[7] Others prefer to confirm laboratory criteria that predict low risk (sometimes including a normal CSF analysis result). Some providers observe the patient very closely without giving antimicrobial therapy; others treat all such infants for 2 days with a single daily dose of ceftriaxone (50 mg/kg) administered parenterally while awaiting the results of blood, urine, and CSF cultures. Either approach, if careful and vigilant, is defensible.

Before an antimicrobial agent is administered, cultures of the blood, urine, and CSF should be obtained. Rapid tests for specific viral pathogens are widely available, can aid decisions about managing patients, and can reduce the duration of hospitalization or eliminate the need.[7,31–33,68] Febrile infants at low risk for serious bacterial infection for whom adequate home observation and follow-up cannot be ensured should be hospitalized and can be observed without antimicrobial treatment. If the child appears well, doing so 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 for complications.[21,27,67]

Most infants with fever who are younger than 1 month should be hospitalized and treated with antimicrobial therapy (with or without acyclovir for herpes simplex virus), although in selected instances, hospitalization without antimicrobial treatment or outpatient management after laboratory evaluations, including CSF analysis, may be reasonable. If a decision is made to administer antimicrobial agents intravenously, ampicillin (100 to 200 mg/kg per day every 6 hours) plus gentamicin (7.5 mg/kg per day every 8 hours) or a third-generation cephalosporin (e.g., ceftriaxone, 50 mg/kg per day in one dose; cefotaxime, 150 mg/kg per day every 8 hours) could be chosen. Ampicillin and gentamicin is a well-established combination with narrower spectrum of antimicrobial activity than ceftriaxone and excellent effectiveness against group B *Streptococcus*, *Listeria monocytogenes,* and many enteric gram-negative rods. Because of the rising incidence of ampicillin-resistant *E. coli* and the rarity of listeriosis in recent large studies, a regimen with a third-generation cephalosporin without ampicillin offers coverage for the few infants who have bacteremia or meningitis with a UTI due to ampicillin-resistant *E. coli*.[11,12,25] No study has directly assessed the relative risks and benefits of either regimen. Before initiating antimicrobial treatment with any regimen, cultures of the blood, urine (obtained by urethral catheterization or suprapubic aspiration of the bladder), and CSF should be obtained.

Children 3 Months of Age and Older

Children 3 months of age and older who appear well and have no apparent focus of infection can be evaluated clinically without laboratory tests or treatment with antimicrobial agents, with the exception of examination of the urine. In the current conjugate vaccine era, blood culture isolates are substantially more likely to be contaminants than to be pathogens.[7] Substantial evidence suggests that obtaining blood cultures routinely from these children has little impact on outcome, although false-positive blood culture results lead to substantial unnecessary costs.[69,70]

The following approach seems appropriate. The febrile child should be carefully assessed for a focus of infection, including UTI, and if a focus is found, the child 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 cefotaxime, 150 mg/kg per day in divided doses every 8 hours, or ceftriaxone, 50 mg/kg once daily) should be initiated; some physicians add vancomycin (40 mg/kg per day in divided doses every 6 to 8 hours). Most of these 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 permit subsequent clinical and laboratory evaluation and antimicrobial treatment as indicated. If a practitioner encounters a febrile child older than 4 months of age who is unimmunized or partially immunized, a more aggressive plan for evaluation and management may be warranted.

Other Considerations

This chapter focuses on invasive bacterial infections, particularly bacteremia, as a cause of fever without apparent focus. Although other serious illnesses such as autoimmune diseases and inflammatory bowel disease can manifest as fever without a focus of infection, they are rare and come to attention because of persistence or recurrence of fever (see Chapter 15).

All references are available online at www.expertconsult.com.

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