

# The Evolving Approach to the Young Child Who Has Fever and No Obvious Source

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Although fever is one of the most common presenting complaints to emergency departments [1], the approach to the febrile young child remains controversial. Despite attempts to simplify and unify the approach to febrile children, the evaluation and treatment of these patients varies considerably [2–4]. Furthermore, recent advances, such as vaccination with the heptavalent pneumococcal conjugate vaccine, warrant the need to reevaluate previously used strategies in the evaluation of the young child who has fever.

The presence of fever worries clinicians and parents alike. Although the differential diagnosis of fever is broad and includes both infectious and non-infectious causes [5], the majority of febrile children have viral infections as sources of their fevers. Febrile young children present a particularly vexing group; when compared with older children, young children are less articulate and less able to localize signs and symptoms, and this age group is the most likely group of children to sustain occult bacterial infections.

Attempts have been made to standardize the approach to the young febrile child. Several algorithmic approaches apply to the evaluation of the young child who has a fever without source (FWS) [6–8]. These patients have traditionally been divided into three subgroups: neonates (birth to 28 days old), young infants (commonly defined as infants between 1 to 3 months of age, although some define this group as children between 1 month and 2 months of

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age), and the older infant or toddler (commonly defined as 3 to 36 months of age, although some studies include patients only up to 24 months old).

### Limitations of current approaches

The approach to the young child who has a FWS has traditionally emphasized the detection of serious bacterial infections such as meningitis, pneumonia, urinary tract infection (UTI), bacterial gastroenteritis, osteomyelitis, and bacteremia. Most viral infections cause self-limited illnesses that do not cause significant morbidity or mortality. Conversely, bacterial infections are more likely to be associated with worse outcomes, a characteristic that has led many to ignore the role of viral infections, especially in the young patient. The role of rapid viral testing in the emergency department, which is becoming increasingly available to emergency clinicians, remains unclear.

Further confusing the approach to these patients is the changing epidemiology of invasive bacterial infections. *Haemophilus influenzae* type b (Hib) previously presented a substantial burden of disease resulting in considerable morbidity and mortality in young children, but, since the early 1990s, universal Hib vaccination has nearly eliminated this organism as a significant cause of disease [9–12].

With the eradication of *Haemophilus influenzae* type b, *Streptococcus pneumoniae* emerged as the predominant bacterial pathogen. In the late 1990s, *S pneumoniae* represented 83% to 92% of positive blood cultures taken from young febrile children presenting to emergency departments, and the overall prevalence of occult bacteremia was 1.6% to 1.9% [9,11]. An effective, 23-valent polysaccharide pneumococcal vaccine has been licensed since 1983, but this vaccine is insufficiently immunogenic in young children and is not recommended for children younger than 2 years of age (the age group at greatest risk for invasive pneumococcal infection).

The heptavalent pneumococcal conjugate vaccine (PCV7), licensed in 2000, covers the seven most common pneumococcal serotypes and has changed the landscape of invasive bacterial disease in young children. The seven serotypes included in this vaccine caused approximately 82% of cases of invasive pneumococcal disease [13]. This vaccine is recommended for universal administration to children younger than 2 years old in a four-dose regimen (doses are given at 2, 4, 6, and 12 to 15 months), as well as to high-risk older children (eg, children who have sickle cell disease, HIV infection, cochlear implants, and other causes of immunocompromise) [14].

This vaccine has been shown to be safe [15,16] and highly effective in preventing invasive pneumococcal disease. In a post licensure surveillance of the Northern California Kaiser Permanente study cohort, the incidence of invasive pneumococcal disease caused by vaccine and cross-reactive vaccine serotypes declined from 51.5 to 98.2 cases of invasive disease per 100,000 person-years in children less than 1 year old to zero cases per 100,000

person-years 4 years after licensure [17]. There was also a reduction of invasive pneumococcal disease in children less than 2 years old, declining from 81.7 to 113.8 cases of invasive disease per 100,000 person-years to zero cases per 100,000 person-years 4 years after the vaccine was licensed [17]. Additionally, there was a decline in invasive pneumococcal disease for all serotypes, not just the seven covered by PCV7, and a significant decline in drug-resistant pneumococci. Moreover, there was a 25% decrease in invasive pneumococcal disease in persons older than 5 years, suggesting herd immunity because these patients were not themselves immunized. These reductions have been replicated in other settings [18–25]. This success has also been reflected in changes in the epidemiology from blood cultures obtained from the emergency department. The incidence of positive blood cultures for all pathogens from emergency department patients is less than 1% [21,25,26].

### **History and physical examination**

The history and physical examination are invaluable in the assessment of the febrile child. A fever is defined as temperature of 38.0°C (100.4°F). Rectal thermometry is considered the gold standard for temperature measurement, because this route is thought to most closely represent the core temperature and is more accurate than oral, axillary, tympanic membrane, and temporal artery thermometry [27–32]. Bundling a young child may increase the skin temperature but probably does not increase the core temperature [33]. Subjective determination of fever by parents at home is moderately accurate [34–36], but further evaluation should be considered in this population because a subjective fever at home may be the only indicator of a potentially serious bacterial infection in a child who is afebrile in the emergency department [37]. Patients who have fevers measured rectally at home should undergo the same evaluation as if these measurements were obtained in the emergency department.

The characteristics of a patient's fever may provide useful information. There is an increase in the rate of pneumococcal bacteremia with an increase in temperature, and this increase is more pronounced in young children [38]. Other studies suggest that the incidence of serious bacterial infections is higher in patients who have hyperpyrexia [39,40]. The duration of the fever at the time of emergency department presentation does not predict whether a child has occult bacteremia [41]. The use of antipyretics should be noted; however, a response (or lack thereof) to antipyretic medications does not predict whether the underlying cause is bacterial or viral [42–46]. Additional important data include associated signs and symptoms, underlying medical conditions, exposure to ill contacts, and immunization status.

An assessment of the child's overall appearance is critical. Although there is an imperfect correlation between physical examination findings and serious bacterial illness, ill-appearing children are more likely than

well-appearing children to have serious bacterial infection, and most well-appearing children do not have serious bacterial infection [47–50]. In the child who has a toxic appearance, an aggressive work-up, antibiotic treatment, and hospitalization are mandated regardless of age or risk factors. The physical examination may reveal obvious sources of infection, and the identification of a focal infection may decrease the need for additional testing. For example, febrile patients who have clinically recognizable viral conditions (eg, croup, chicken pox, and stomatitis) have lower rates of bacteremia than patients who have no obvious source of infection [51].

With the exception of neonates and young infants, if a child has a non-toxic appearance, a more selective approach can be undertaken. When a child who has a febrile illness has an obviously identifiable cause, the treatment and disposition should generally be tailored to this specific infection. The approach to the young child who has a FWS is discussed in the following sections.

### **Neonates: birth to 28 days old**

Neonates are at particularly high risk for serious bacterial infection (Fig. 1). Although most febrile neonates presenting to the emergency department are diagnosed ultimately as having a nonspecific viral illness, approximately 12% to 28% of all febrile neonates presenting to a pediatric emergency department have serious bacterial illness [52–54]. Neonates are infected typically by more virulent bacteria such as group B *Streptococcus*, *Escherichia coli*, and *Listeria monocytogenes*. Group B *Streptococcus*, a common bacterial pathogen in this age group, is associated with high rates of meningitis (39%), non-meningeal foci of infection (10%), and sepsis (7%) [55]. Although only a small percentage of neonates are infected by *S pneumoniae*, these neonates have a mortality rate of 14% [56]. The most common bacterial infections in this age group are UTIs and occult bacteremia [52,54]. Neonates are more likely to experience serious sequelae from viral infections (eg, herpes simplex virus [HSV] meningitis).

#### *Evaluation of the febrile neonate*

Traditional risk stratification strategies have used ancillary testing to supplement the limited information available from the history and physical examination. Unfortunately, it is difficult to predict accurately which neonates have invasive disease, even when laboratory testing is used. Initial studies by Dagan and colleagues [57,58] appeared promising. The “Rochester criteria” were applied to infants less than 90 days old, and neonates were included. Using these criteria, Jaskiewicz and colleagues [59] found that 2 of 227 children younger than 30 days old who met low-risk criteria had serious bacterial infection. Ferrera and colleagues [60] found that 6% of neonates who were retrospectively classified as low risk by the Rochester criteria had serious bacterial infection.

Baker and colleagues retrospectively stratified neonates into high- and low-risk patients based on the “Philadelphia criteria” [61] they had derived for older infants. The neonates who were placed in the high-risk category had a higher incidence of bacterial disease (18.6%), but 4.6% of neonates who were classified as low-risk patients had serious bacterial infections. Additionally, 11 different bacterial pathogens were identified in 32 patients who had serious bacterial infections, and only 1 of these 32 patients was infected with *S pneumoniae*. Kadish and colleagues [54] found a similar rate of serious bacterial infections in neonates whom they categorized as low risk when they retrospectively applied both the Philadelphia criteria and similar criteria created by Baskin and colleagues (the “Boston criteria”). They also found a wide range of bacterial pathogens, but only two cultures in 55 patients who had serious bacterial infection were positive for *S pneumoniae*. Chiu and colleagues [53,62] have also demonstrated low but significant rates of serious bacterial infections in neonates initially classified as low risk.

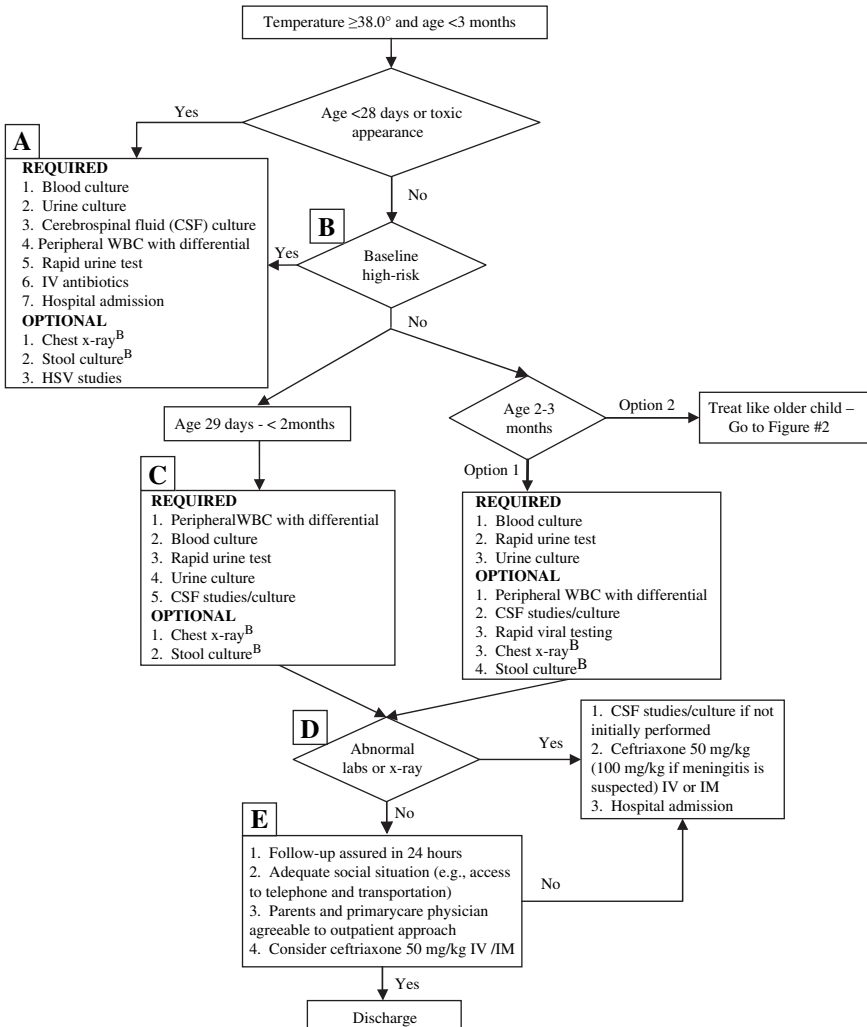
Because of the inability of the physical examination to accurately predict serious infections in neonates, recommendations for these patients include obtaining blood cultures, urine for rapid urine testing, urine cultures, and cerebrospinal fluid (CSF) studies [6]. A peripheral white blood cell (WBC) count is often ordered in the evaluation of febrile neonates, but the discriminatory value of the WBC count is insufficient to differentiate between patients who have serious bacterial infections and those who do not [63,64]. Because of the inability of the WBC count to predict bacteremia, blood cultures should be ordered for all patients. Although various options for rapidly testing for UTI exist (eg, urine dipstick, standard urinalysis, and enhanced urinalysis), no rapid test detects all cases of UTI; therefore, urine cultures must be ordered for all of these patients [65,66]. Urine should be collected by bladder catheterization or suprapubic aspiration because bag urine specimens are associated with high rates of contamination [67–70]. Because the peripheral WBC is a poor screening test for meningitis [71], a lumbar puncture should be performed in all febrile neonates. Chest radiographs are indicated only in the presence of respiratory symptoms, and stool analyses are indicated only in the presence of diarrhea. In neonates, the presence of signs suggestive of viral illness does not negate the need for a full diagnostic evaluation. Unlike in older children, in whom documented respiratory syncytial virus (RSV) infections decrease the likelihood of serious bacterial illness, RSV-infected neonates have the same rate of serious bacterial infection when compared with RSV-negative neonates [72].

#### *Treatment and disposition of the febrile neonate*

Because of the high rates of serious bacterial infections, all febrile neonates should receive antibiotics. Typically, these patients are treated with a third-generation cephalosporin or gentamicin. Ceftriaxone is not recommended for neonates who are jaundiced because of the concern for inducing

unconjugated hyperbilirubinemia [73,74]. Other third-generation cephalosporins, such as cefotaxime, 50 mg/kg intravenously (75–100 mg/kg if there is a concern for meningitis based on CSF results), or gentamicin, 2.5 mg/kg intravenously, are used in this age group. Additionally, although the incidence of *L monocytogenes* is low [75], ampicillin, 50 mg/kg intravenously (100 mg/kg intravenously if there is a concern for meningitis) is still recommended in the empiric treatment of these patients [76].

Neonatal HSV infections occur in approximately 1 in 3200 deliveries in the United States [77]. Neonates who have HSV infections usually present within the first 2 weeks of life, and only a minority of infected children have fever [78]. Rates of morbidity and mortality are high with neonatal



HSV, but treatment with high-dose acyclovir (20 mg/kg intravenously) improves outcomes in patients [79]. Acyclovir is not recommended routinely for empiric treatment in addition to standard antibiotics in febrile neonates [78] but should be considered in febrile neonates with risk factors for neonatal HSV. Risk factors include primary maternal infection, especially for neonates delivered vaginally, prolonged rupture of membranes at delivery, the use of fetal scalp electrodes, skin, eye, or mouth lesions, seizures, and CSF pleocytosis [77,80,81].

Febrile neonates should be hospitalized regardless of the results of laboratory studies. Outpatient management of these patients has been suggested and occurs frequently when patients present to pediatricians' offices [37]; however, given the lack of prospective studies addressing this approach as well as the limitations inherent in the screening evaluation in the emergency department and the difficulties in arranging follow-up evaluation, hospitalization is strongly recommended.

### Young infants: 1 to 2 or 3 months old

The approach to febrile young infants, defined most commonly as children less than 2 or 3 months old, changed dramatically in the 1980s and early 1990s (see Fig. 1). Before this time, most febrile young infants presenting to academic medical centers were hospitalized and frequently started on antibiotic therapy [82]. This aggressive approach was based, in part, on the



Fig. 1. Fever without an apparent source in children less than 3 months of age. (A) Urine testing can be accomplished by microscopy, Gram stain, or urine dipstick. Chest radiographs are indicated in patients who have hypoxia, tachypnea, abnormal lung sounds, or respiratory distress. Stool studies are indicated in patients who have diarrhea. HSV testing should be considered in the presence of risk factors (see text for details). HSV testing is best accomplished by polymerase chain reaction or viral culture. Neonates should receive both ampicillin (50 mg/kg intravenously; 100 mg/kg intravenously if concern for meningitis) and cefotaxime (50 mg/kg; 100 mg/kg intravenously if concern for meningitis) or gentamicin (2.5 mg/kg intravenously). Older children should receive ceftriaxone (50 mg/kg intravenously; 100 mg/kg intravenously if concern for meningitis). (B) Young patients who have increased underlying risk include children who were premature, who had prolonged hospital stays after birth, those who have underlying medical conditions, patients who have indwelling medical devices, patients who have a fever greater than 5 days, and patients already on antibiotics. (C) Urine testing can be accomplished by microscopy, Gram stain, or urine dipstick. Chest radiographs are indicated in patients who have hypoxia, tachypnea, abnormal lung sounds, or respiratory distress. Stool studies are indicated in patients who have diarrhea. (D) Abnormal laboratory values are as follows: peripheral WBC count,  $< 5000/\text{mm}^3$  or  $> 15,000/\text{mm}^3$  or band-to-neutrophil ratio  $> 0.2$ ; urine testing,  $\geq 5$  WBC/hpf, bacteria on Gram stain, or positive leukocyte esterase or nitrite; CSF,  $\geq 8$  WBC/ $\text{mm}^3$  or bacteria on Gram stain; stool specimen,  $\geq 5$  WBC/hpf; chest radiograph, infiltrate on chest film. (E) Administering ceftriaxone (50 mg/kg intravenously or intramuscularly) is optional but should be considered in patients who have undergone lumbar puncture. Patients who have not undergone lumbar puncture should not be given ceftriaxone. (Adapted in part from Ishimine P. Fever without source in children 0 to 36 months of age. *Pediatr Clin N Am* 2006;53:184; with permission.)



relatively limited amount of information obtainable from the examination of young infants [83] and the high morbidity rate observed with *H influenzae* type b infection. Several decision rules were developed in an attempt to identify febrile young children who were believed to be at low risk for serious bacterial infection and who could be treated on an outpatient basis.

The Rochester criteria stratified children less than 60 days old into high- and low-risk groups. The children who met the low-risk criteria appeared well, had been previously healthy, and had no evidence of skin, soft tissue, bone, joint, or ear infections. Additionally, these children had normal peripheral WBC counts (5000–15,000/mm<sup>3</sup>), normal absolute band counts ( $\leq 1500/\text{mm}^3$ ),  $\leq 10$  WBC/high-power field (hpf) of centrifuged urine sediment, and, for those patients who have diarrhea,  $\leq 5$  WBC/hpf on stool smear [57,58]. The low-risk group identified children who were unlikely to have serious bacterial infections, with a negative predictive value of 98.9% [59].

Baskin and colleagues [84] described the Boston criteria for febrile children between 1 and 3 months of age who presented to the emergency department with temperatures  $\geq 38.0^\circ\text{C}$ . Infants were discharged after an intramuscular injection of ceftriaxone, 50 mg/kg, if they generally appeared to be well (not strictly defined) and had no ear, soft tissue, joint, or bone infections on physical examination. Furthermore, these patients had to have CSF with  $\leq 10$  WBC/hpf, microscopic urinalysis with  $\leq 10$  WBC/hpf or a urine dipstick negative for leukocyte esterase, a peripheral WBC count of  $\leq 20,000/\text{mm}^3$ , and normal findings when a chest radiograph was obtained (all tests except the chest radiograph were performed on all patients). Twenty-seven of 503 children (5.4%) were later found to have serious bacterial infection (bacterial gastroenteritis, UTI, and occult bacteremia).

Baker and colleagues [85] developed the Philadelphia criteria and similarly sought to identify low-risk patients between 29 and 56 days old with temperatures of  $\geq 38.2^\circ\text{C}$ . Patients who appeared to be well (as defined by an Infant Observation Score of 10 or less) had a peripheral WBC count of  $\leq 15,000/\text{mm}^3$ , a band-to-neutrophil ratio of  $\leq 0.2$ , a urinalysis with fewer than 10 WBC/hpf, few or no bacteria on a centrifuged urine specimen, CSF with fewer than 8 WBC/mm<sup>3</sup>, a gram-negative stain, negative results on chest radiographs (obtained on all patients), negative stool findings for blood, and few or no WBCs on microscopy (ordered for patients who had watery diarrhea). These patients were considered to have a negative screen and were not treated with antibiotics. Of the 747 consecutively enrolled patients, 65 (8.7%) had serious bacterial infections. All 65 patients who had serious bacterial infections were identified using these screening criteria. In a follow-up study (in which fever was defined as  $\geq 38.0^\circ\text{C}$  rectally) of 422 consecutively enrolled febrile young infants, 43 (10%) had serious bacterial infections, and all 101 patients who were identified as low risk had no serious bacterial infections. All 43 patients who had serious bacterial infections were identified prospectively as high risk using the Philadelphia criteria [86].



The most common bacterial infections in this age group are UTIs; correspondingly, the most common bacterial pathogen identified is *E coli* [61,84,86]. In the large studies by Baskin and Baker and colleagues [84], only a minority of patients who had serious bacterial infection had pneumococcal infection; therefore, children in this age group are unlikely to benefit directly from the PCV7 vaccine. In the Baskin study, only one of nine patients who had occult bacteremia in this study was infected with *S pneumoniae*. Four of 70 bacterial infections were caused by *S pneumoniae* in Baker's original study [61].

### *Evaluation of the febrile young infant*

Because relying solely on the clinical examination results in a substantial number of missed serious bacterial infections, laboratory testing is required in this age group. A catheterized urinalysis and blood and urine cultures should be obtained in all patients. Although an abnormally high or low WBC count increases the concern for bacteremia or meningitis, it is an imperfect screening tool for bacteremia and meningitis, and the decision to obtain blood cultures and spinal fluid should not depend on the results of the WBC count [63,64,71]. Stool studies for WBC counts and stool cultures should be ordered in patients who have diarrhea. Chest radiographs should be obtained only in young febrile infants who have signs of pulmonary disease (tachypnea  $\geq 50$  breaths/min, rales, rhonchi, retractions, wheezing, cough, grunting, nasal flaring, or cough) [87,88].

The results of these tests help to risk stratify these young children. The WBC count is considered abnormal if it is greater than  $15,000/\text{mm}^3$  or less than  $5000/\text{mm}^3$ , or if the band-to-neutrophil ratio is greater than 0.2. There should be fewer than 8 WBC/ $\text{mm}^3$  and no organisms on Gram stain of the CSF. The urine is considered abnormal if the urine dipstick is positive for nitrite or leukocyte esterase, if there are  $\geq 5$  WBC/hpf on microscopy, or if organisms are seen on a Gram-stained sample of uncentrifuged urine. If obtained, there should be fewer than 5 WBC/hpf in the stool specimen and no evidence of pneumonia on a chest radiograph [6].

The need for lumbar puncture is controversial in this age group. Although the Boston and Philadelphia criteria require CSF analysis, the Rochester criteria do not mandate lumbar puncture. The rarity of bacterial meningitis contributes to the controversy surrounding the utility of the lumbar puncture. The prevalence of bacterial meningitis in febrile infants less than 3 months old is 4.1 cases per 1000 patients, and neither the clinical examination nor the peripheral WBC count is reliable in diagnosing meningitis in this age group [63,71]; therefore, lumbar puncture should be strongly considered. Additional controversy surrounds the need for antibiotics in patients who are identified as low risk. Patients identified as low risk by the Philadelphia protocol were not given antibiotics, whereas patients enrolled in the Boston study were given intramuscular ceftriaxone.

There is some concern that performing a lumbar puncture in a bacteremic patient may lead to meningitis [89,90]. Four of 8300 children 3 months of age or less who underwent CSF analysis had bacterial meningitis and  $\leq 8$  WBC/mm<sup>3</sup> in the CSF [91], and clinical decision rules to determine which children who have CSF pleocytosis have bacterial infection are less accurate in this young age group [92]. Published recommendations state that parenteral antibiotics should be “considered” if a lumbar puncture is performed [6].

The presence of a documented viral infection lowers but does not eliminate the likelihood of a serious bacterial infection in this age group. Young infants classified as high-risk patients using the Rochester criteria who had test-proven viral infection (enterovirus, respiratory virus, rotavirus, and herpes virus) were at lower risk for serious bacterial infection when compared with patients who did not have an identified source (4.2% versus 12.3%) [93]. A subgroup analysis of 187 febrile infants 28 to 60 days old from the largest prospective multicenter study of RSV infection in young infants showed a significantly lower rate of serious bacterial infection in RSV-positive patients when compared with RSV-negative patients (5.5% versus 11.7%) [72], confirming the results of similar studies in young infants who had bronchiolitis. Most of these bacterial infections were UTIs [94,95]. These studies were underpowered to detect differences in rates of bacteremia and meningitis between RSV-positive and RSV-negative patients. Based on available data, it remains unclear whether the clinician can forgo blood and spinal fluid testing in RSV-positive infants. Patients less than 90 days old who have enteroviral infections have a similar rate of concurrent serious bacterial infections (mostly UTI) of 7% [96].

#### *Treatment and disposition of the febrile young infant*

Most infants who have a FWS who are otherwise healthy and born at full term, who are well appearing, and who have normal laboratory values can be managed on an outpatient basis. If the patient undergoes a reliable follow-up within 24 hours, if the parents have a way of immediately accessing health care if there is a change in the patient's condition, and if the parents and the primary care physician understand and agree with this plan of care, the patient may be discharged home. Ceftriaxone, 50 mg/kg intravenously or intramuscularly, can be given before discharge, but withholding antibiotics in these low-risk patients is acceptable as well. Patients who do not undergo lumbar puncture in the emergency department should not receive antibiotics because this will confound the evaluation for meningitis if the patient is still febrile on follow-up examination. Close follow-up reevaluation must be ensured before discharge.

For patients who have abnormal test results or who appear to be ill, antibiotic therapy and hospitalization are warranted. Ceftriaxone, 50 mg/kg intramuscularly or intravenously (100 mg/kg if meningitis is suspected), is commonly used for these patients. Additional antibiotics should be

considered in select circumstances (eg, ampicillin or vancomycin for suspected infection by *Listeria*, gram-positive cocci, or *Enterococcus*). Some studies suggest that patients in this age group who have UTIs may be treated on an outpatient basis [97,98]; however, no large prospective studies provide evidence as to the safety of outpatient management in this age range. Young infants who are RSV positive are at higher risk of serious complications, such as apnea [99], and the clinician must evaluate this concern in addition to the risks of serious bacterial infection when making a disposition decision.

#### *Older infants and toddlers: 3 months and older*

A temperature of 38.0°C defines a fever and is the usual threshold at which diagnostic testing is initiated in the young infant; however, in febrile children 3 months and older (some studies extend this group to include 2-month-old infants), a temperature of 39.0°C is commonly used as the temperature for initiating further evaluation (Fig. 2). This higher temperature cutoff is used because of the increasing risk of occult pneumococcal bacteremia with increasing temperatures [38] and because large studies of occult bacteremia, widely referenced in the medical literature, use this temperature as the study entry criteria [9,11,100]. No systematic studies have been conducted in the post-PCV7 era to determine whether an increasing height of fever is still correlated with increasing rates of bacterial infection. Although the rates of serious bacterial infection may be higher in children who have temperatures  $\geq 39.0^{\circ}\text{C}$ , these patients may still have occult infections with lower heights of fever.

#### *Evaluation of the child 3 months and older*

The history is often helpful in this age group. Patients are more likely to be able to communicate complaints, and the physical examination is more informative. Clinical assessment as to whether a child appears to be well, ill, or toxic is important. A well appearance does not completely exclude bacteremia [101], but children who appear toxic are much more likely to have serious illness when compared with ill- or well-appearing children (92% versus 26% versus 3%, respectively) [102]. Many bacterial infections can be identified by history and physical examination alone, but some infections may be occult. The most common serious bacterial infections in this age group that may not be clinically apparent are bacteremia, UTI, and pneumonia. Rapid influenza testing may result in a decreased need for diagnostic testing [103]; febrile children between 3 and 36 months who are influenza A positive are less likely to have serious bacterial infections than children who are influenza A negative [104]. If no focal infection is identified and the cause is not believed to be viral, diagnostic testing in this age group is undertaken for the purposes of identifying occult bacterial infections.

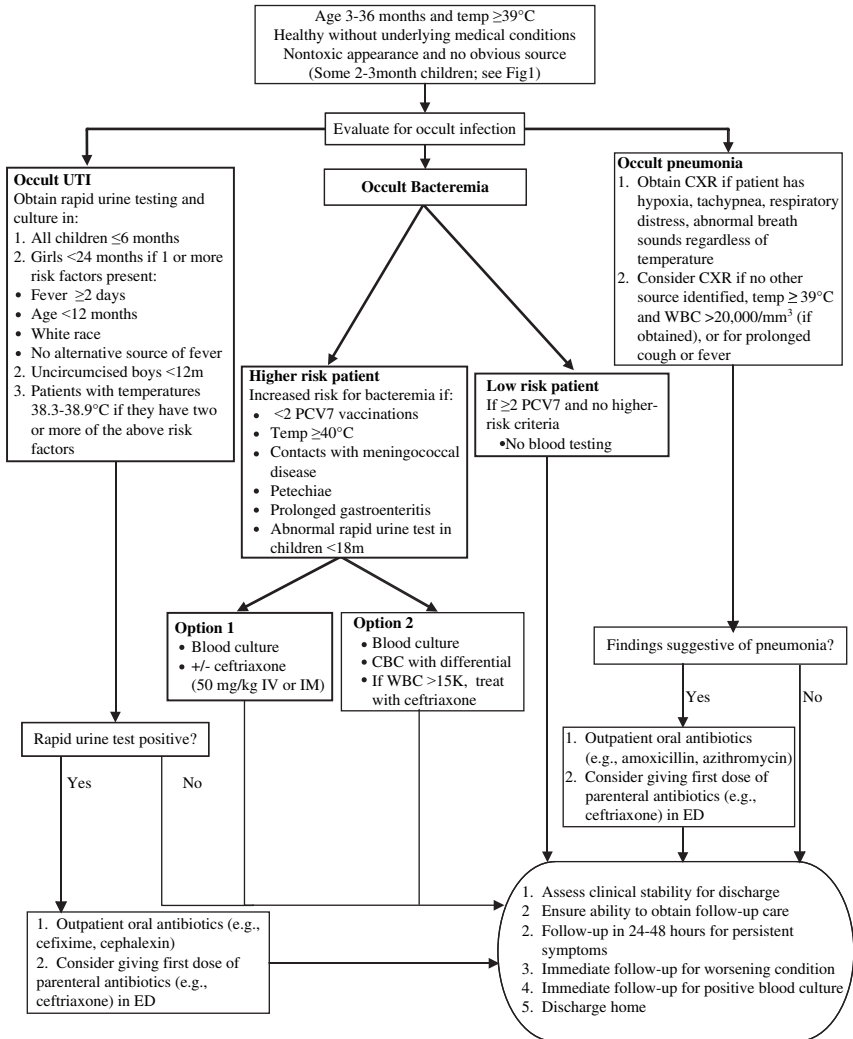


Fig. 2. Fever without apparent source in children 3 to 36 months of age. CBC, complete blood count; CXR, chest radiography; ED, emergency department. (Adapted in part from Ishimine P. Fever without source in children 0 to 36 months of age. *Pediatr Clin N Am* 2006;53:186.)

### Occult bacteremia

In the pre-PCV7 era, the children at greatest risk for occult bacteremia were 6 to 24 months old, and the most common pathogen was *S pneumoniae* [9,11]. In the era of universal PCV7 vaccination, the overall incidence of pneumococcal bacteremia (and, accordingly, the total overall incidence of bacteremia) has dropped substantially. In a population immunized with PCV7, *E coli* bacteremia is at least as common as pneumococcal bacteremia.

This changing epidemiology has added to the confusion regarding the utility of blood testing in the evaluation of the febrile child, specifically regarding the value of blood testing in the identification of occult bacteremia. Although there is an increased risk of bacteremia with an increasing WBC count, the sensitivity and specificity of a WBC count  $\geq 15,000/\text{mm}^3$  is only 74% to 86% and 55% to 77%, respectively [11,21,105,106]. Similarly, patients who had *E coli* bacteremia were more likely to have elevated WBC counts when compared with control subjects without bacteremia; however, the WBC counts in patients who have *Salmonella* [21], *Staphylococcus aureus* [21], and *Neisseria meningitidis* [107] bacteremia do not differ from that in control patients without bacteremia. Using an elevated WBC or absolute neutrophil count as a surrogate marker for occult bacteremia means that many patients will unnecessarily receive antibiotics and a substantial number of patients who have bacteremia will be untreated.

The shifting epidemiology of bacteremia has prompted cost-effectiveness analyses of various management strategies. Using pre-PCV7 data, Lee and colleagues analyzed five strategies for the 3- to 36-month-old febrile child who did not have an identifiable source of infection. In their sensitivity analysis, they found that when the prevalence rate of pneumococcal bacteremia dropped to 0.5%, which is essentially the current rate of pneumococcal bacteremia in emergency departments [21,25,26,108], clinical judgment (eg, patients who were deemed to be at low risk clinically for occult pneumococcal bacteremia received no testing or antibiotics) was the most cost-effective strategy [109].

The role of antibiotics in children believed to be at high risk for bacteremia is controversial as well. Currently, there is no way of prospectively identifying bacteremic patients. Practically, this means that, at the time of the emergency department visit, many febrile children who are at risk for bacteremia must be treated to prevent a single serious bacterial infection. Before PCV7, the use of amoxicillin [110] and ceftriaxone [100,105] appeared to shorten the duration of fever in bacteremic febrile children. Nevertheless, there is a paucity of randomized, placebo-controlled data demonstrating that the use of either oral or parenteral antibiotics prevents significant adverse infectious sequelae in these children. One study compared amoxicillin with placebo for the treatment of febrile children and showed no difference in the rates of subsequent focal infection [110], but another retrospective study demonstrated that, in patients ultimately found to have bacteremia, treatment with oral or parenteral antibiotics reduced persistent fever, persistent bacteremia, and hospital admission [111]. A subsequent meta-analysis has shown that, although ceftriaxone prevents serious bacterial infection in patients who had proven occult bacteremia, 284 patients at risk for bacteremia would need to be treated with antibiotics to prevent one case of meningitis [112]. Complicating this analysis is the fact that in a majority of patients who have pneumococcal bacteremia, the bacteremia will resolve spontaneously [9]. Focal infections develop in 15% of bacteremic children [9], and meningitis develops

in 2.7% to 5.8% of patients who have occult pneumococcal bacteremia [112,113]. These analyses were conducted on data obtained in the pre-PCV7 era, and similar risk-benefit analyses have not been conducted after the introduction of PCV7. Nonetheless, it is clear that with the significant decrease in invasive pneumococcal disease [17,24,114], many more children will be treated unnecessarily with antibiotics to prevent a single serious outcome.

PCV7 has led to remarkable declines in the rates of invasive pneumococcal disease. Declines in the rate of invasive disease occur even when the four-dose regimen is incomplete, and even one dose of PCV7 offers some protection, although one dose given before 6 months of age did not seem to protect against illness occurring after 6 months or more [115]. Although maximum individual protection against the seven serotypes covered by this vaccine occurs after completion of the four-dose immunization regimen (the standard immunization regimen entails doses at age 2 months, 4 months, 6 months, and 12 to 15 months) [116], similarly high rates of vaccine efficacy in protecting against serotype disease were noted in two- and three-dose immunization regimens as well [115]. Among the seven serotypes, the amount of disease reduction is variable [18,20,117]. Although the overall rate of invasive pneumococcal disease is declining, the rates of invasive disease caused by nonvaccine serotypes appear to be stable and may be increasing [24,27,118–120]. The clinical implications of this serotype replacement are unclear.

In addition to pneumococcus, another common cause of bacteremia is *E coli*. *E coli* bacteremia is more common in children aged less than 12 months and is most common in children 3 to 6 months of age. *E coli* bacteremia is commonly associated with a concomitant UTI [121]; in one recent study, all 27 patients identified with *E coli* bacteremia had UTIs [21]. *Salmonella* causes 4% to 8% of occult bacteremia, occurring in 0.1% of all children 3 to 36 months old who have temperatures  $\geq 39.0^{\circ}\text{C}$  [9,11,21,100]. Although the majority of patients who have *Salmonella* bacteremia have gastroenteritis, 5% will have primary bacteremia [122]. One large retrospective study of children who have non-typhi *Salmonella* bacteremia showed that 54% of bacteremic children had temperatures less than  $39.0^{\circ}\text{C}$  (29% of patients were afebrile) and a median WBC count of  $10,000/\text{mm}^3$ . These children had a 41% rate of persistent bacteremia on follow-up cultures, and the rates of persistent bacteremia were the same in patients who were treated with antibiotics at the initial visit and those who were not. Among immunocompetent patients, 2.5% of patients who had *Salmonella* bacteremia had focal infections, and no differences in rates of focal infection were noted in children older and younger than 3 months of age [123].

Meningococcal infections are infrequent causes of bacteremia but are associated with high rates of morbidity and mortality [124]. *Neisseria meningitidis* is a leading cause of bacterial meningitis [125]. Combining the data from Boston and Philadelphia occult bacteremia studies, 0.02% of children who appeared to be nontoxic and who had temperatures  $\geq 39.0^{\circ}\text{C}$  had meningococcal disease [9,11]. Usually, these patients are overtly sick; however,

12% to 16% of patients who have meningococcal disease have unsuspected infection [107,126]. Although there is an association between younger age and elevated band count with meningococcal disease, the positive predictive values of these variables are low given the low prevalence of this disease, and the researchers in one large meningococcal disease study believe that routine screening for all young febrile children who have complete blood counts for meningococcal bacteremia is not useful [107]. Patients who had unsuspected meningococcal disease who were treated empirically with antibiotics had fewer complications than patients who were untreated, but there were no differences in rates of permanent sequelae or death [127]. Nevertheless, testing and empiric treatment may be warranted for children at higher risk for meningococcal disease. Risk factors for meningococcal bacteremia include contact with patients who have meningococcal disease, periods of meningococcal disease outbreaks, and the presence of fever and petechiae (although most children who have fever and petechiae do not have invasive bacterial disease) [128–130]. A new tetravalent meningococcal conjugate vaccine was licensed for use in the United States in 2005. Although clinical trials in infants and young children are in progress, this vaccine has been licensed and recommended for routine administration in children 11 years old and older [131].

Children who have positive blood cultures need to be reexamined. A child who has a positive blood culture with any pathogen who appears ill needs a repeat blood culture, lumbar puncture, intravenous antibiotics, and hospital admission. Because the rates of spontaneous clearance of pneumococcal bacteremia are high, patients who have pneumococcal bacteremia who are afebrile on repeat evaluation can be observed on an outpatient basis [132] after repeat blood cultures are obtained and these patients are given antibiotics. Children who have pneumococcal bacteremia and who are persistently febrile need repeat blood cultures and generally should undergo lumbar puncture and require hospital admission. The treatment and disposition for well-appearing children who have *Salmonella* bacteremia are less clear, but patients with meningococcal bacteremia should be hospitalized for parenteral antibiotics [106]. Furthermore, the approach to the patient who has an *E coli* UTI who later grows *E coli* in a blood culture is unclear, although repeat assessment and blood culture should be performed, and consideration should be given to lumbar puncture and admission.

Contaminated blood cultures are common, and in younger children, the rate of contaminated cultures frequently exceeds the rate of true positive cultures [9,11,21,25,108,133]. False-positive blood cultures lead to further testing and unnecessary use of antibiotics and hospitalizations [134], along with the attendant iatrogenic complications [135].

Given the observed decline in invasive pneumococcal disease, the inconsistent relationship between the height of a fever and rates of bacteremia, the strong association between *E coli* UTIs and *E coli* bacteremia, the relative infrequency of meningococcemia and *Salmonella* bacteremia, and the limited value of the WBC count in predicting the latter two diseases, the



need for a routine complete blood count, blood cultures, and empiric antibiotics has been called into question in fully immunized children [21,25,136,137]. If the clinician decides to obtain blood testing, the most important test is the blood culture, because this is the gold standard test for bacteremia. At best, the WBC count is a limited screening tool, and an abnormality is a relatively poor surrogate marker for bacteremia. It is reasonable to address parental preferences when devising a “risk-minimizing” versus a “test-minimizing” [138] approach to these children, because parental perceptions and preferences regarding risk may differ from those of the treating clinician [139–141].

### *Occult urinary tract infection*

UTIs are common sources of fever in young children, and these children are at risk for permanent renal damage from such infections. In older children, historical and examination features such as dysuria, urinary frequency, and abdominal and flank pain may suggest UTI; however, in young children, symptoms are usually nonspecific. Although the overall prevalence in children is 2% to 5% [142–144], certain subgroups of children are at higher risk for UTIs. White race, girls, uncircumcised boys, children who have no alternative source of fever, and temperatures  $\geq 39.0^{\circ}\text{C}$  are associated with a higher risk of UTI. Sixteen percent of white girls less than 2 years old with temperatures  $\geq 39.0^{\circ}\text{C}$  and a FWS had UTI [143,144]. UTIs were found in 2.7% to 3.5% of febrile children, even when there were other potential sources of fever (eg, gastroenteritis, otitis media, upper respiratory tract infection, and nonspecific rash) [143,144].

Gorelick and Shaw [145] derived a clinical decision rule which has been subsequently validated for febrile girls with temperatures  $\geq 38.3^{\circ}\text{C}$  who are less than 24 months of age. Urine testing is indicated if two or more of the following risk factors are present: age less than 12 months, fever for 2 or more days, temperature  $\geq 39.0^{\circ}\text{C}$ , white race, and no alternative source of fever. This rule has a sensitivity of 95% to 99% and a false-positive rate of 69% to 90% in detecting girls with UTI [145,146]. No similar clinical decision rules exist for boys, but, because the prevalence in boys less than 6 months old is 2.7% [144], urine should be collected in all boys in this age group. The prevalence of UTIs in uncircumcised boys is eight to nine times higher than in circumcised boys; therefore, uncircumcised boys younger than 12 months should also undergo urine testing [144,147,148].

Several rapid urine tests have good sensitivity for detecting UTIs. Enhanced urinalysis ( $\geq 10$  WBC/hpf or bacteria on Gram-stained, uncentrifuged urine) [65,149] and a combination of  $\geq 10$  WBC/hpf and bacteriuria (on either centrifuged or uncentrifuged urine) [150] are both excellent screening tests. The more readily available urine dipstick (positive for either leukocyte esterase or nitrites) has a sensitivity of 88% [65]. Because no rapid screening test detects all UTIs, urine cultures should be ordered for all of

these patients [68]. Any positive test results from a rapid test should lead to a presumptive diagnosis of a UTI, and antibiotic treatment should be initiated. Most patients who have UTIs and appear well can be treated on an outpatient basis. Empiric antibiotic therapy should be tailored to local bacterial epidemiology, but reasonable outpatient medications include cefixime (8 mg/kg twice on the first day of treatment, then 8 mg/kg/d starting from the second day) or cephalexin (25–100 mg/kg/d divided into four doses). The duration of therapy should be from 7 to 14 days.

### *Occult pneumonia*

Young children commonly develop pneumonia, and the most common pathogens are viruses and (based on pre-PCV7 data) *S pneumoniae* [151]. The diagnosis of pneumonia based on clinical examination can be difficult [152]. Multiple attempts have been made at deriving clinical decision rules for the accurate diagnosis of pneumonia, but none has been successfully validated [153–155]. The presence of any pulmonary findings on examination (eg, tachypnea, crackles, respiratory distress, or decreased breath sounds) increases the likelihood of pneumonia, and, conversely, the absence of these findings decreases the likelihood of pneumonia [156–158]. The role of pulse oximetry in detecting pneumonia is unclear [159,160]. Although the chest radiograph is often believed to be the gold standard, there is variability in the interpretation of radiographs even by pediatric radiologists [161]. Furthermore, radiographic findings cannot be used to reliably distinguish between bacterial and nonbacterial causes [162,163].

Some cases of pneumonia are likely to be clinically occult. In the pre-PCV7 era, Bachur and colleagues found that 19% to 26% of children younger than 5 years old who had a temperature of  $\geq 39.0^{\circ}\text{C}$ , a WBC count  $\geq 20,000/\text{mm}^3$ , and no other source or only a “minor” bacterial source on examination had a pneumonia infection as seen on a chest radiograph [164]. This study has been criticized because of a high degree of interobserver variability in chest radiograph interpretation, because of the failure to perform a WBC count on over half the infants who had a temperature  $\geq 38^{\circ}\text{C}$ , and because the majority of clinical assessments were performed by residents. Furthermore, a retrospective study at the same institution after universal PCV7 vaccination showed a 5% “occult” (ie, no respiratory distress, no tachypnea or hypoxia, and no lower respiratory tract abnormalities on examination) pneumonia rate in patients selected to undergo chest radiography [165]. A clinical policy guideline from the American College of Emergency Physicians states that, although there is insufficient evidence to determine when a chest radiograph is required, the clinician is advised to “consider” a chest radiograph in children older than 3 months who have a temperature  $\geq 39^{\circ}\text{C}$  and a WBC count  $\geq 20,000/\text{mm}^3$ . Furthermore, a chest radiograph is usually not indicated in febrile children older than 3 months who have a temperature  $< 39^{\circ}\text{C}$  without clinical evidence of acute

pulmonary disease [87]. The British Thoracic Society similarly recommends that a chest radiograph should be considered in children younger than 5 years old who have a temperature  $\geq 39^{\circ}\text{C}$  caused by an unclear source of infection [166]. These recommendations may change based on the decline of the prevalence of pneumococcal pneumonia [167]. A chest radiograph should be obtained in all febrile children regardless of fever height if there are physical examination findings suggestive of pneumonia, such as tachypnea, increased work of breathing, asymmetric or abnormal breath sounds, or hypoxia.

No decision rules exist for pediatric pneumonia that help with disposition decisions in children who have pneumonia, but the majority of patients are treated on an outpatient basis. Both amoxicillin (80 mg/kg/d divided twice or three times daily) and macrolide antibiotics (eg, azithromycin, 10 mg/kg by mouth on the first day, then 5 mg/kg/d for 4 more days) are acceptable. Treatment duration is usually from 7 to 10 days (with the exception of azithromycin), but no definitive evidence supports a specific duration of therapy [166].

### **Future directions and questions**

The pneumococcal vaccine has already had a significant impact on the epidemiology of bacterial infection in young children, and this vaccine seems to have had some impact on the practice patterns of pediatricians. Pediatricians who were surveyed ordered fewer blood and urine tests and were less likely to prescribe antibiotics in a hypothetical scenario of an 8-month-old febrile but otherwise healthy infant when the child had been fully immunized with PCV7 versus when they had not been immunized [168]. The number of blood cultures ordered by pediatricians (but not by emergency physicians) has fallen by 35% in the Northern California Kaiser Permanente system [21].

Although the decline in invasive pneumococcal disease has been dramatic, the rise in nonvaccine serotype pneumococcal disease raises concerns [118,169]. Likewise, there is an increase in antibiotic resistance in nonvaccine serotype pneumococci [19,120,170]. Newer pneumococcal conjugate vaccines with increased serotype coverage are in development [171].

Despite the use of the PCV7 vaccine, bacteremia will still develop in patients; therefore, there remains a need for better tests to diagnose invasive bacterial disease. Several additional tests are being studied as potential surrogate markers for bacterial disease in young children: procalcitonin, C-reactive protein, and interleukin-6 [172–180].

### **Summary**

Most children aged 0 to 36 months who have a FWS have viral infections, but certain subsets of febrile children are at higher risk for more serious bacterial disease. The child who appears to be toxic, regardless of age,

needs a comprehensive work-up, antibiotic coverage, and admission to the hospital. Generally, this work-up entails a complete blood count with differential, blood culture, urinalysis and urine culture, lumbar puncture with CSF analysis, Gram stain and culture, and, when indicated, chest radiographs and stool studies. These patients should receive broad-spectrum parenteral antibiotics before hospital admission. Additionally, the approach to patients who are immunocompromised (eg, sickle cell disease, cancer, or long-term steroid use), who have indwelling medical devices (eg, ventriculoperitoneal shunts and indwelling venous access catheters), who are currently taking antibiotics, or who have prolonged fevers should be individualized.

The febrile neonate (0–28 days old) is at high risk for serious bacterial infection, even with a benign examination and normal screening laboratory results; therefore, these patients also need a complete blood count with differential, blood culture, urinalysis and urine culture, lumbar puncture with CSF analysis, Gram stain and culture, and, when indicated, chest radiographs and stool studies. Febrile neonates should receive empiric antibiotic coverage, typically with ampicillin (50 mg/kg intravenously, or 100 mg/kg if meningitis is suspected) and cefotaxime (50 mg/kg intravenously, or 100 mg/kg if meningitis is suspected) or gentamicin (2.5 mg/kg intravenously).

The febrile young infant (1–3 months old) is also at significant risk for bacterial infection. These patients need complete blood counts, blood cultures, urinalyses, and urine cultures. A lumbar puncture with CSF analysis, Gram stain, and culture should be strongly considered because other laboratory tests such as the WBC count are inaccurate in predicting which patients have meningitis. When clinically indicated, chest radiographs and stool studies should be obtained as well. If any of these test findings are abnormal (including a peripheral WBC  $\geq 15,000/\text{mm}^3$  or  $\leq 5000/\text{mm}^3$ , a band-to-neutrophil ratio  $\geq 0.2$ , a urine dipstick test positive for nitrite or leukocyte esterase or a finding of  $\geq 5$  WBCs/hpf or organisms seen on Gram stain, CSF fluid with  $\geq 8$  WBC/ $\text{mm}^3$  or organisms on Gram stain,  $\geq 5$  WBC/hpf in the stool specimen, or evidence of pneumonia on a chest radiograph), the patient should receive ceftriaxone (50 mg/kg intravenously or intramuscularly, or 100 mg/kg intravenously if meningitis is suspected) and should be admitted to the hospital. If these initial laboratory results are normal, the patient can be discharged if follow-up within 24 hours can be ensured. The administration of ceftriaxone, 50 mg/kg intravenously or intramuscularly, should be considered if a lumbar puncture is performed; if a lumbar puncture is not performed, antibiotics should be withheld. If a patient is 2 to 3 months old and the practitioner is comfortable with his or her pediatric assessment skills, these children can be treated similarly to older febrile children.

The older infant or toddler (3–36 months old) who has a temperature of  $\geq 39.0^\circ\text{C}$  may be treated more selectively. In this age group, if no febrile source is identified definitively, a catheterized urine specimen for evaluation (dipstick, urinalysis, microscopy, or Gram stain) and urine culture should be

obtained in girls less than 2 years old if one or more of the following risk factors are present: age less than 12 months, fever for 2 or more days, white race, and no alternative source of fever. Urine testing should also be considered in girls who have temperatures of 38.3°C to 39.0°C if they meet two of the previous risk factors. All boys younger than 6 months and all uncircumcised boys younger than 12 months should also have catheterized urine sent for rapid urine testing and culture. Chest radiographs should be considered in children who have physical examination findings suggestive of pneumonia. Additionally, a chest film should be considered in a child with an unexplained peripheral WBC count  $\geq 20,000$  (if obtained), or with prolonged fever or cough.

Patients who have not received at least two PCV7 vaccinations should still be considered to be susceptible to pneumococcal bacteremia, but these children benefit to some degree from herd immunity conferred by the population as a whole. Based on pre-PCV7 data, the most cost-effective approach to the child who has had fewer than three PCV7 doses is to obtain a peripheral WBC count. If the WBC count is  $\geq 15,000/\text{mm}^3$ , a blood culture should be ordered, and the administration of ceftriaxone should be considered [109]; however, other options (eg, blood culture with or without empiric antibiotic administration, or a WBC count and blood culture with selective antibiotic administration) are also reasonable. This approach should also be considered when parents are unsure of their child's immunization status, because parental recall of immunization status is relatively inaccurate [181].

Blood testing should be considered optional in patients who have received two or more PCV7 vaccinations, because the rate of bacteremia in this population is less than 1%. This approach is acceptable because of the low overall rates of bacteremia, the limited accuracy of the WBC count in predicting bacteremia, and the high rate of spontaneous resolution of pneumococcal bacteremia. Additional benefits of this approach include forgoing the discomfort and expense of testing, as well as the complications associated with false-positive results (which are more likely than true-positive results). This approach presumes that the clinician and the parents accept the risk of missing some cases of occult bacteremia with the attendant risk of morbidity. Although an elevated complete blood count can be suggestive of pneumococcal and *E coli* bacteremia, this is neither a sensitive nor specific test. Furthermore, the complete blood count is unhelpful as a screen for other types of occult bacteremia. Empiric antibiotic therapy is generally not indicated for these patients; however, if the clinician chooses to obtain a complete blood count and this is elevated, or if there is any other concern for an increased risk of bacteremia (eg, hyperpyrexia [40]), blood cultures and antibiotics should be considered.

No combination of clinical assessment and diagnostic testing will successfully identify all patients who have serious infection at the time of initial presentation; therefore, the importance of timely reassessment (even for the

child with initially normal test results or the child who has received antibiotic therapy) cannot be overemphasized, and caretakers must be instructed to return to the emergency department or primary care provider's office immediately for any deterioration in the child's condition. A systematic plan for the evaluation and treatment of the febrile child may help reduce unnecessary testing and morbidity associated with serious infection; however, no single strategy can capture the nuances of all febrile young patients. Any standardized approach to the febrile young child should serve as an adjunct to, and not a replacement for, the judgment of the treating clinician.

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