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Fever Without Source in Children 0 to 36 Months of Age

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Fever, one of the most common chief complaints of children seeking medical attention [1,2], prompted over 5 million emergency department (ED) visits in 2002 [3]. Most of these children have identifiable causes of their fevers, but many will have fever without an apparent source (FWS) after conclusion of the history and physical examination. Despite the frequency of fever as a chief complaint, there is considerable controversy in the management of the young child who has FWS [4–8]. The challenge in the evaluation of the febrile young child lies in balancing the minimization of risk to the patient with the costs of testing and treatment.

Definition of fever

A variety of temperatures have been used to define fever, but the most commonly accepted definition of fever is a temperature of $\geq$38.0°C (100.4°F), a value derived from studies by Wunderlich, who took 1 million measurements on 25,000 patients and determined that this temperature was the upper limit of normal [9]. Although less invasive means of measuring temperature exist, such as axillary and aural thermometry, the variability of measurements at these sites [10–12] warrants using the current outpatient reference standard, rectal thermometry, when measuring temperatures in young children. An accurate temperature measurement is especially important if a practitioner chooses to use fever guidelines because the implementation of these guidelines is initiated once a patient meets a certain temperature threshold.

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Once it is determined that a child has a fever, measured in the emergency department or in the practitioner's office, further evaluation can then proceed. However, a child who presents with a reported fever at home but who is afebrile in the ED or in the office poses more of a challenge. Parents may not be able to accurately define fever [13], and subjective assessment by parents has been shown to have generally good but variable sensitivity in the detection of fever [14–16]. Parental assessment is often colored by "fever phobia," inaccurate concerns and misconceptions about the potential danger of fever [17,18]. Additionally, bundling of infant creates confusion for both providers and parents because bundling of infants may raise the skin temperature but not rectal temperature [19]. However, a fever measured at home with rectal thermometry generally warrants the same concern as a fever measured in the ED or in the office. Six of 63 patients with bacteremia or bacterial meningitis in a large office-based study of young febrile infants were found to be afebrile in physicians' offices but were febrile at home [20].

Epidemiology

The management of the febrile young child continues to evolve. Contributing to this confusion is the changing epidemiology of bacterial infection in young children. *Haemophilus influenzae* previously presented a significant burden of disease, resulting in substantial morbidity and mortality in young children. *H influenzae* represented 19% of all positive cultures in febrile children who presented to a pediatric walk-in clinic in 1972 [21], but after widespread use of the *H influenzae* type b vaccine starting in 1991, the epidemiology of invasive bacterial disease changed dramatically. *H influenzae* type b has been nearly eliminated [22,23], with a 94% decline in *H influenzae* meningitis shortly after the introduction of the Hib vaccine [24]. Combining the results of two large studies of occult bacteremia in patients seen in the mid 1990s in Boston and Philadelphia, there were no blood cultures that grew *H influenzae* from 15,366 patients seen in these pediatric emergency departments [25,26].

Corresponding to the decrease in invasive disease caused by *H influenzae*, there has been an increase in the percentage of invasive diseases caused by *Streptococcus pneumoniae*. The burden of disease caused by *S pneumoniae* has been significant. *S pneumoniae* represented 83% to 92% of positive blood cultures taken from young febrile children presenting to EDs in the mid 1990s, and the overall prevalence of occult bacteremia was 1.6% to 1.9% [25,26]. In 1998, there were an estimated 12,560 cases of invasive pneumococcal disease (bacteremia, meningitis, and pneumonia) and 110 deaths in children younger than 2 years of age, with a case fatality rate of 1.4% [27]. This low overall case fatality rate likely reflects the generally good outcomes in patients with bacteremia, which represented 75% of the invasive disease in this population [27]. However, the case fatality rate resulting from *S pneumoniae* meningitis is higher than

meningitis caused by *Neisseria meningitidis*, *Streptococcus* group B, *Listeria monocytogenes*, or *H influenzae* [24]. Additionally, there has been an increasing prevalence of multidrug resistant *S pneumoniae*, and the proportion of isolates with multidrug resistance is highest in children under 5 years of age [28,29]. Although an effective, 23-valent polysaccharide pneumococcal vaccine has been licensed since 1983, this vaccine is insufficiently immunogenic in young children and is, therefore, ineffective and not recommended for children younger than 2 years of age, which is the age group most at risk for invasive pneumococcal infection.

The introduction of the heptavalent pneumococcal conjugate vaccine (PCV7), covering the seven most common pneumococcal serotypes, has changed the landscape of invasive bacterial disease in young children. There are over 90 pneumococcal serotypes that have been identified, but the seven serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F) cause approximately 82% of the cases of invasive pneumococcal disease [27]. This vaccine, licensed in 2000, is recommended for universal administration to children younger than 2 years old in a 4-dose regimen (doses are given at 2, 4, 6, and 12–15 months), as well as to high-risk older children (eg, children with sickle cell disease, chronic cardiac and pulmonary diseases, and other immunocompromising conditions) [30].

This vaccine has been shown to be both safe [31] and highly effective in preventing invasive pneumococcal disease, with a prelicensure study demonstrating an efficacy of 97% [32]. In a postlicensure surveillance of the Northern California Kaiser Permanente [32] study cohort, the cohort that served as the largest prelicensure study group of the PCV7 vaccine, 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 0 cases per 100,000 person-years 4 years after licensure [33]. 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 0 cases per 100,000 person-years 4 years after the vaccine was licensed [33]. There was a decline in invasive pneumococcal disease for all serotypes, not just the seven covered by PCV7, with a decline of 94% and 91% in children less than 1 year of age and 2 years of age, respectively. There was also a significant decline in drug-resistant pneumococci and a 25% decrease in invasive pneumococcal disease in people older than 5 years old, suggesting herd immunity because these patients were not themselves immunized. These declines occurred despite the fact that only 24% of children less than 2 years old received all four recommended doses because of a vaccine shortage [33].

These findings have been replicated in other settings. In Massachusetts, there was a 69% decline in the incidence of total invasive pneumococcal disease as well as an 88% decline in non-meningitis vaccine-serotype disease [34]. Similarly, there was a 69% decline in the total incidence of invasive pneumococcal disease and a 78% decline in the incidence of disease caused by vaccine serotypes, seen in a national network of regional surveillance centers administered

by the Centers for Disease Control and Prevention, accompanied by a decline in penicillin-resistant pneumococcal isolates [35]. There was a 66% decline in the incidence of invasive pneumococcal infections (77% decline in vaccine-covered serotypes) noted from a network study of children's hospitals [36]. Three likely mechanisms are involved in the PCV7-associated decrease in disease: individual risk decline, decline in antibiotic-resistant bacteria, and herd immunity.

Caveats

Although the differential diagnosis of fever is quite broad and includes both infectious and noninfectious causes [37], the majority of febrile children have underlying infectious causes of fever. For the purposes of this article, patients are presumed to be febrile from infectious sources. Additionally, diagnostic strategies emphasize the detection of bacterial disease because bacterial diseases are more likely to be associated with worse outcomes, but viral infections can also be associated with significant morbidity and mortality, especially in younger children.

Most large studies addressing serious bacterial illness use children from large, urban, tertiary care children's hospital emergency departments. Physicians in primary care settings are less compliant with ED-derived recommendations for the evaluation and treatment of febrile children, but compared with ED patients, outcomes for these patients are similar [20,38]. This similarity in outcome may be the result of several causes: the sickest patients may preferentially present to the ED, patients may get closer follow-up by their primary care providers, the judgment of primary care providers may be more sensitive than criteria put forth in various guidelines, or because the likelihood of serious disease in these children is low [39].

Finally, most studies of febrile young children exclude patients who have potentially complicating risk factors. These studies typically have excluded children who are immunocompromised (eg, sickle cell disease, cancer, or long-term steroid use), have indwelling medical devices (eg, ventriculoperitoneal shunts and indwelling venous access catheters), are currently taking antibiotics, or have prolonged fevers (≥ 5 days).

Approach to the young febrile child

History and physical examination

The history and physical examination are invaluable in the assessment of the febrile child. The level and duration of a child's fever as well as the mode of temperature measurement are important to note. There is an increase in the prevalence of pneumococcal bacteremia with an increase in temperature [40], and this is more pronounced in young children. In children less than 3 months of age

who have temperatures $\geq 40.0^{\circ}C$, 38% have serious bacterial infection [41]. The duration of the fever itself at the time of ED presentation does not predict whether a child has occult bacteremia [42]. The use of antipyretics should be noted. Parents often give inaccurate doses of antipyretics [43,44], and paradoxically, in one study, patients treated with antipyretics presented to the ED with higher temperatures than those patients who were untreated at home [45]. A response (or lack thereof) to antipyretic medications does not predict whether the underlying cause is bacterial or viral [45–49]. 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. If a child appears to be toxic, this mandates an aggressive work-up, antibiotic treatment, and hospitalization, 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 with recognizable viral conditions (eg, croup, chickenpox, and stomatitis) have lower rates of bacteremia than patients with no obvious source of infection [50]. Similarly, febrile children with influenzavirus A have lower rates of serious bacterial infections compared with febrile children without influenzavirus A [51]. Febrile patients with otitis media appear to have the same rate of bacteremia as febrile children without otitis media [52,53].

With the exception of neonates and young infants, if a child has a nontoxic 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 FWS is discussed below.

Age-specific considerations

The approach to the young child who has a fever without a source varies depending on the age of the child. Traditionally, young children have been categorized in into three distinct age groups for the purposes of fever evaluation: the neonate (0–28 days old), the young infant (commonly defined as infants between 1 and 3 months of age, although some authors define this group to include children only between 1 and 2 months of 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 in this group). Although the use of chronologic age distinctions are somewhat artificial (for example, the difference in the risk of serious bacterial illness is likely to be inconsequentially different between a 28-day-old child and a 29-day-old child), there is some rationale behind these seemingly arbitrary age distinctions. Younger children have decreased immunologic function and are more commonly infected with virulent organisms. Additionally, the physical examination is more difficult because young children have a limited behavioral repertoire.

Young infants: 0 to 3 months old

The traditional approach to young infants has included aggressive investigation, antibiotic administration, and hospital admission [54]. However, the hospitalization of young infants can result in iatrogenic complications, financial ramifications, and parental stress [55,56]. Recently, this approach has been challenged, and the current recommendations are not as strict regarding mandatory admission in well-appearing infants over 28 days old.

Neonates: birth to 28 days old

Neonates are at a particularly high risk for SBI. The majority of febrile neonates presenting to the ED are diagnosed ultimately as having a nonspecific viral illness, but approximately 12% of all febrile neonates presenting to a pediatric emergency department have serious bacterial illness [57,58]. When they are infected, neonates are infected typically by more virulent bacteria (eg, *Streptococci* group B, *Escherichia coli*, and *L monocytogenes*) and are more likely to develop serious sequelae from viral infections (eg, herpes simplex virus meningitis). *Streptococci* group B, a common bacteria pathogen in this age group, is associated with high rates of meningitis (39%), non-meningeal foci of infection (10%), and sepsis (7%) [59]. This age group is the least likely to be affected by the use of the pneumococcal vaccine because only a small percentage of neonates are infected by this pathogen. Although infection is uncommon, those neonates who are infected with *S pneumonia* have a mortality rate of 14% [60]. The most common bacterial infections in this are group are urinary tract infections (UTIs) and occult bacteremia [57,58].

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 [61,62] appeared promising. These ''Rochester criteria'' (Rochester, Boston, and Philadelphia criteria are discussed below) were applied to infants less than 90 days old, and neonates were included. Using the Rochester criteria, Jaskiewicz and colleagues [63] found that 2 of 227 children younger than 30 days old who met low-risk criteria had SBI. However, Ferrera and colleagues [64] found that 6% of neonates who were retrospectively classified as low risk by the Rochester criteria had SBI.

Baker and colleagues [65] retrospectively stratified neonates into high- and low-risk patients based on the ''Philadelphia criteria'' 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 a serious bacterial infection. Additionally, 11 different

bacterial pathogens were identified in 32 patients with SBI, and only one of these 32 patients was infected with *S pneumoniae*. Kadish and colleagues [58] found a similar rate of SBI 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 with SBI were positive from *S pneumoniae.*

Because of the inability to accurately predict serious infections in this age group, the recommendations for these patients include obtaining blood cultures, urine for rapid urine testing, urine cultures, and cerebrospinal fluid (CSF) [66,67]. 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 with SBI versus nonbacterial infection [68–70]. Because of the inability of the white blood cell count to predict SBI, blood cultures should be ordered on all patients. Although various options for rapidly testing for urinary tract infection exist (eg, urine dipstick, standard urinalysis, and enhanced urinalysis), no rapid test detects all cases of UTI, so urine cultures must be ordered in all of these patients [71,72]. Urine should be collected by bladder catheterization or suprapubic aspiration because bag urine specimens are associated with unacceptably high rates of contamination [73,74]. 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 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 SBI compared with RSV-negative neonates [75].

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 have jaundice because of the concern for inducing unconjugated hyperbilirubinemia [76–78]. Other third-generation cephalosporins, such as cefotaxime, 50 mg/kg intravenously (IV) (100 mg/kg if there is a concern for meningitis based on CSF results), or gentamicin, 2.5 mg/kg IV, are used in this age group. Additionally, although the incidence of *L monocytogenes* is quite low [79], ampicillin, 50 mg/kg IV (100 mg/kg IV if there is a concern for meningitis) is still recommended in the empiric treatment of these patients [80].

Neonatal herpes simplex virus (HSV) infections occur in approximately 1 per 3200 deliveries in the United States [81]. Neonates with HSV infections usually present within the first 2 weeks of life, and only a minority of infected children have fever [82]. Rates of morbidity and mortality are high with neonatal HSV, but

treatment with high-dose acyclovir improves outcomes in patients [83]. Acyclovir is not recommended routinely for empiric treatment in addition to standard antibiotics in febrile neonates [82] but should be considered in febrile neonates with risk factors for neonatal HSV (20 mg/kg IV). Risk factors include primary maternal infection, especially those neonates delivered vaginally, prolonged rupture of membranes at delivery, the use of fetal scalp electrodes, skin, eye or mouth lesions, seizures, and CSF pleocytosis [81,84,85].

Febrile neonates should be hospitalized, regardless of the results of laboratory studies. Outpatient management of these patients has been suggested [86] and occurs frequently when patients present to pediatricians' offices [20]. 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 frequent difficulties in arranging follow-up evaluation, hospitalization is strongly recommended [66,67].

Young infants: 1 to 3 months old

The approach to febrile young infants, defined most commonly as children less than either 2 or 3 months old (in this discussion, age less than 3 months will be used), changed dramatically in the 1980s and early 1990s. Before this time, most febrile young infants presenting to academic medical centers were hospitalized and frequently started on antibiotic therapy. The aggressive approach was based in part on the relatively limited amount of information obtainable from examination of young infants [65,87], the high morbidity rate observed with *H influenzae* type b infection, and the efficacy of antibiotics in the treatment of serious bacterial infection.

The "Rochester criteria" put forth by Dagan and colleagues [61,62] stratified children less than 60 days old into high- and low-risk groups. The children who met these criteria appeared well, had been previously healthy, and had no evidence of skin, soft tissue, bone, joint, or ear infection. Additionally, the children had normal peripheral WBC count (5000–15,000/mm^3), normal absolute band counts ($\leq$ 1500/mm^3), $\leq$ 10 WBC/high-power field (hpf) of centrifuged urine sediment, and for those patients with diarrhea, $\leq$ 5 WBC/hpf on stool smear [61,62]. The low-risk group identified children who were unlikely to have serious bacterial infection, with a negative predictive value of 98.9% [63].

In 1992, Baskin and colleagues [88] 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°C. Infants were discharged after an intramuscular (IM) injection 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 UA with $\leq$ 10 WBC/hpf or urine dipstick negative for leukocyte esterase, a peripheral WBC count of $\leq$ 20,000/mm^3, and normal findings in patients in whom 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, urinary tract infection, and occult bacteremia). Only one of nine patients with occult bacteremia in this study were infected *S pneumoniae* [88].

Baker and colleagues [65] similarly sought to identify low-risk patients between 29 and 56 days old with temperatures of $\geq 38.2^{\circ}C$. Patients who appeared to be well (as defined by an Infant Observation Score of 10 or less), had a peripheral WBC count of $\leq 15{,}000/mm^3$, a band-to-neutrophil ratio of ≤ 0.2, a urinalysis (UA) with fewer than 10 WBC/hpf, few or no bacteria on a centrifuged urine specimen, CSF with fewer than 8 WBC/mm^3, a gram-negative stain, negative results on chest radiographs (obtained on all patients), and stool negative for blood and few or no WBCs on microscopy (ordered on those patients with watery diarrhea) were considered to have a negative screen and were not treated with antibiotics. Of the 747 consecutively enrolled patients, 65 (8.7%) had SBI. All 65 patients who had serious bacterial infection were identified using these screening criteria. These 65 patients had a total of 70 bacterial infection sites where a bacterial pathogen was identified, and four of these 70 infections were caused by *S pneumoniae* [65]. In a follow-up study (in which fever was defined as $\geq 38.0^{\circ}C$ rectally) of 422 consecutively enrolled febrile young infants, 43 (10%) had SBI, and all 101 patients who were identified as low risk had no SBI. All 43 patients who had SBI were identified prospectively as high risk using the Philadelphia criteria [89].

In the large studies by Baskin and Baker and colleagues, only a minority of patients with SBI had pneumococcal infection, and thus, children in this age group are unlikely to benefit directly from the PCV7 vaccine [65,88].

Evaluation of the febrile young infant

The clinical evaluation alone will result in a substantial number of missed SBI, so laboratory testing is required in this age group. The white blood cell count with differential, catheterized urinalysis, and blood and urine cultures should be obtained in all patients. Stool studies for white blood cell counts and stool cultures should be ordered in patients with diarrhea. Chest radiographs should be obtained only in young febrile infants with signs of pulmonary disease (tachypnea ≥ 50 breaths/minute, rales, rhonchi, retractions, wheezing, coryza, grunting, nasal flaring, or cough) [90,91].

Controversies in this age group surround the need for lumbar puncture. 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. However, the prevalence of bacterial meningitis in febrile infants less than 3 months old is 4.1 per 1000 patients, and neither the clinical examination nor the peripheral white blood cell count is reliable in diagnosing meningitis in this age group [68,92]; therefore, the LP 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 studies were given intramuscular ceftriaxone. There is some concern that performing a lumbar puncture in a bacteremic patient may lead to meningitis [93,94], and published recommendations state that parenteral antibiotics should be "considered" if a lumbar puncture is performed [66].

The results of these tests help to risk-stratify these young children. The WBC count is considered abnormal if the count is $\geq 15{,}000/mm^3$ or $\leq 5000/mm^3$ and the band- to-neutrophil ratio is ≥ 0.2. The urine is considered abnormal if the urine dipstick is positive for nitrite or leukocyte esterase; or there are ≥ 5 WBC/hpf on microscopy; or organisms are seen on a Gram-stained sample of uncentrifuged urine. If obtained, there should be fewer than 5 WBC/hpf on the stool specimen, no evidence of pneumonia on chest x-ray, and fewer than 8 WBC/mm^3 and no organisms on Gram stain of the cerebrospinal fluid [66]. Of note, however, one recent study reported that four of 8300 children who underwent CSF analysis had bacterial meningitis and ≤ 8 WBC/mm^3 in the CSF [95].

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 documented viral infection (enterovirus, respiratory virus, rotavirus, and herpesvirus) were at lower risk for SBI compared with patients who did not have an identified source (4.2% versus 12.3%) [96]. Similarly, a subgroup analysis of 187 febrile infants 28 to 60 days old showed a significantly lower rate of SBI in RSV-positive patients compared with RSV-negative patients (5.5% versus 11.7%) [75], confirming the results of similar studies in young infants who had bronchiolitis. Most of these bacterial infections were urinary tract infections [97,98]. Patients less than 90 days old who have enteroviral infections have a rate of concurrent serious bacterial infections (mostly UTI) of 7% [99].

Treatment and disposition of the febrile young infant

Assuming that the patient is an otherwise healthy term infant who appears to be well and who does not have any lab abnormalities, outpatient management may be considered. If the patient undergoes a reliable follow-up within 24 hours, the parents have a way of immediately accessing health care if there is a change in the patient's condition, and the parents and the primary care physician understand and agree with this plan of care, then the patient may be discharged home. The use of ceftriaxone, 50 mg/kg IV or IM, before discharge is acceptable, as is withholding antibiotics in these low-risk patients. Patients who did not undergo lumbar puncture in the ED 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 assured before discharge.

For those patients who have abnormal test results or who appear to be ill, antibiotic therapy and hospitalization are warranted. Ceftriaxone, 50 mg/kg IM or IV (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 urinary tract infections may be treated on an outpatient basis [100,101]; however, there are no prospective studies with a large number of young infants that address this question.

Older infants and toddlers: 3 to 36 months old

A temperature of $\geq 38.0^{\circ}C$ defines a fever, and in younger children, this temperature is the usual threshold beyond which diagnostic testing is initiated. However, in febrile children between 3 and 36 months old (some studies extend this group to include 2-month-old infants), a temperature of $\geq 39.0^{\circ}C$ is commonly used as the threshold temperature for initiating further evaluation. This higher temperature cutoff is used because of the increasing risk of occult bacteremia with increasing temperatures [40]. Large studies of occult bacteremia, widely referenced in the medical literature, use this temperature as the study entry criteria [25,26,102].

Evaluation of the child 3 to 36 months old

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 [103], but children who appear toxic are much more likely to have serious illness compared with ill- or well-appearing children (92% versus 26% versus 3%, respectively) [104]. Many bacterial infections can be identified by history and physical examination alone, but some infections may be occult. The serious bacterial infections that may not be clinically apparent are bacteremia, urinary tract infection, and pneumonia. If no focal source of infection is identified and the cause is not believed to be viral, then diagnostic testing in this age group is undertaken for the purposes of identifying these occult bacterial infections.

Occult bacteremia

In the era before universal PCV7 vaccination, the pathogen that most commonly caused occult bacteremia was *S pneumoniae* [25,26]. The children at greatest risk for pneumococcal bacteremia are children between 6 and 24 months old. There has been much controversy about the role of blood testing in the evaluation of the febrile child, specifically regarding the value of blood testing in the identification of occult bacteremia. There is an increased risk of bacteremia

with an increasing white blood cell count [26,105,106], but the sensitivity and specificity of a white blood cell count $\geq 15{,}000/mm^3$ is only 80% to 86% and 69% to 77%, respectively. An absolute neutrophil count (ANC) of $\geq 10{,}000/mm^3$ is a stronger predictor of occult bacteremia than an elevated white blood cell count. Eight percent of patients who have an ANC $\geq 10{,}000/mm$ have occult pneumococcal bacteremia, whereas 0.8% of patients who have an ANC $\leq 10{,}000/mm^3$ have occult pneumococcal bacteremia [40]. Nevertheless, using an elevated WBC or ANC as a surrogate marker for occult bacteremia means that many patients will unnecessarily receive antibiotics.

The shifting epidemiology of bacteremia has prompted cost-effectiveness analyses of various management strategies. Using pre-PCV7 data, Lee and colleagues [107] analyzed five strategies for the 3- to 36-month-old febrile child who did not have an identifiable source of infection. Using a bacteremia prevalence rate of 1.5%, the authors concluded that the most cost-efficient strategy was to obtain CBCs and to selectively send blood cultures and treat patients empirically for WBC counts $>15{,}000/mm^3$. In their sensitivity analysis, the authors found that when the prevalence rate of pneumococcal bacteremia dropped to 0.5%, then clinical judgment (eg, the patient who was deemed to be at low risk clinically for occult pneumococcal bacteremia received no testing) was a more cost-effective strategy.

The role of antibiotics in children believed to be at high-risk for bacteremia is controversial as well. There is currently no way of prospectively identifying bacteremic patients, and practically, this means that at the time of the ED or office visit, many febrile children who are at risk for bacteremia must be treated to prevent a single serious bacterial infection. The use of both amoxicillin [108] and ceftriaxone [102,105] appears to shorten the duration of fever in bacteremic febrile children. However, 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 [108]. 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 [109]. A subsequent meta-analysis has shown that, although ceftriaxone prevents serious bacterial infection in patients with proven occult bacteremia, 284 patients at risk for bacteremia would need to be treated with antibiotics to prevent one case of meningitis [110]. Although oral antibiotics also decrease the risk of SBI in patients with occult bacteremia caused by *S pneumoniae*, it is unclear whether antibiotics reduce the risk of meningitis in these patients [111]. Additionally, there is no apparent difference in rates of serious bacterial infection in patients with occult pneumococcal bacteremia who are treated with oral versus parenteral antibiotics [112]. Complicating this analysis is the fact that in a majority of patients with pneumococcal bacteremia, the bacteremia will resolve spontaneously [25]. Focal infections develop in 17% of bacteremic children [25], and 2.7% to 5.8% of patients with occult

pneumococcal bacteremia develop meningitis [111,113]. These analyses were conducted on data obtained in the pre-PCV7 era, and it is likely, with the significant decrease in invasive pneumococcal disease, that many more febrile patients will need to be treated to prevent SBI.

There are relatively few data on occult bacteremia in the post-PCV7 era. In one retrospective cohort study of pediatric emergency department patients, three of 329 blood cultures in children between 2 to 36 months old were positive for S *pneumoniae.* One patient was infected with a nonvaccine serotype, one was not immunized with PCV7, and a third patient was infected with an unknown serotype [114].

Although pneumococcus has been the most common cause of occult bacteremia, other causes of bacteremia can be occult as well. *Salmonella* causes 4% of occult bacteremia, occurring in 0.1% of all children 3 to 36 months old who have temperatures $\geq 39.0^{\circ}C$ [25,26,102], and whereas the majority of patients with *Salmonella* bacteremia have gastroenteritis, 5% will have primary bacteremia [115]. One large retrospective study of non-*typhi Salmonella* bacteremia in children showed that 54% of bacteremic children had a temperature $\leq 39.0^{\circ}C$ and a median WBC count of 10,000/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 with *Salmonella* bacteremia had focal infections, and no difference in rates of focal infection were noted in children older and younger than 3 months of age [116].

Meningococcal infections are infrequent causes of bacteremia but are associated with high rates of morbidity and mortality. Combining the data from Boston and Philadelphia occult bacteremia studies, 0.02% of children who appeared to be nontoxic and had temperatures $\geq 39.0^{\circ}C$ had meningococcal disease [25,26]. Usually, these patients are overtly sick; however, 12% to 16% of patients with meningococcal disease have unsuspected infection [117,118]. Although there is an association between younger age and elevated band count with meningococcal disease, the positive predictive values of these variables are quite low, given the low prevalence of this disease, and authors of one large meningococcal disease study believe that routine screening for all young febrile children with CBCs for meningococcal bacteremia is not useful [117]. 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 [119]. However, testing and empiric treatment may be warranted for children at higher risk for meningococcal disease. Risk factors for meningoccal bacteremia include contact with patients with meningoccal disease, periods of meningoccal disease outbreaks, and presence of fever and petechiae (although the majority of children with fever and petechiae do not have invasive bacterial disease) [120–122]. 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 only in children 11 years old and older [123].

Children who have positive blood cultures need to be reexamined. A patient who appears ill needs a repeat blood culture, lumbar puncture, intravenous antibiotics, and hospital admission. Patients with pneumococcal bacteremia who are afebrile on repeat evaluation can be followed on an outpatient basis [124] after repeated blood cultures and 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 with *Salmonella* bacteremia are less clear, but patients with meningococcal bacteremia should be hospitalized for parenteral antibiotics [106].

Contaminated blood cultures are common, and in younger children, the rate of contaminated cultures frequently exceeds the rate of true positive cultures [25,26,114,125,126]. Although the average cost to the patient of a false-positive blood culture is rather small [127], false-positive blood cultures lead to further testing, use of antibiotics, and hospitalizations [128], along with the attendant iatrogenic complications [129]. The rates of blood culture contamination decline when cultures are drawn from a separate site rather than through a newly inserted intravenous catheter [126].

Given the observed decline in invasive pneumococcal disease, the relative infrequency of meningococcemia and *Salmonella* bacteremia, and the limited value of the white blood cell count in predicting the latter two diseases, the need for routine CBC, blood cultures, and empiric antibiotics have been called into question in fully immunized children [130,131]. Baraff, the author of the commonly referenced fever algorithms [66,132], has recently stated that children who have received three does of vaccine are at sufficiently low risk that they do not need blood testing or antibiotics and that patients who have received only two doses of the Hib and PCV7 vaccines are not at any significant risk for occult bacteremia [133]. It is reasonable to address parental preferences when devising a ''risk-minimizing'' versus a ''test-minimizing'' [134] approach to these children because parental perceptions and preferences regarding risk may differ from those of the treating clinician.

Occult urinary tract infection

UTIs are common sources of fever in young children, and children are at risk for permanent renal damage from UTIs. In older children, historical and examination features such as dysuria, urinary frequency, and abdominal and flank pain may suggest urinary tract infection. However, in young children, symptoms are usually nonspecific. Although the overall prevalence in children is 2% to 5% [135–137], certain subgroups of children are at higher risk for UTIs. Whites, girls, uncircumcised boys, no alternative source of fever, and temperatures $\geq 39.0^{\circ}C$ were associated with a higher risk; 16% of white girls less than 2 years

old with temperatures ≥39.0°C and fever without source had urinary tract infections [135,136]. 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) [135,136].

Based on these prevalence data, a clinical decision rule was derived and validated for febrile girls 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 ≥ 39.0°C, white, and no alternative source of fever [138]. This rule has a sensitivity of 95% to 99% and a false-positive rate 69% to 90% in detecting girls with UTI [138,139]. No similar clinical decision rules exist for boys, but because the prevalence in boys less than 6 months old is 2.7% [136], urine should be collected in all boys in this age group. The prevalence of UTIs in uncircumcised boys is 8 to 9 times higher than circumcised boys, so uncircumcised boys younger than 12 months old should also undergo urine testing [136,140,141].

Urine culture is the gold standard for the diagnosis of urinary tract infection, but results are not immediately available. Several rapid urine tests have very good sensitivity for detecting UTIs. Enhanced urinalysis (≥10 WBC/hpf or bacteria on Gram stained, uncentrifuged urine) [71,142] or a combination of ≥ 10 WBC/hpf and bacteriuria (on either centrifuged or uncentrifuged urine) [143] are both excellent screening tests. The more readily available urine dipstick (positive for either leukocyte esterase or nitrites) has a sensitivity of 88% [71]. Importantly, however, because no rapid screening test detected all UTIs, urine cultures should be ordered on all of these patients [74]. Any positive test results from a rapid test should lead to a presumptive diagnosis of a urinary tract infection, and antibiotic treatment should be initiated. Most patients with urinary tract infection who 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* [144]. The diagnosis of pneumonia based on clinical examination can be difficult [145]. Multiple attempts have been made at deriving clinical decision rules for the accurate diagnosis of pneumonia, but none has been successfully validated [146–148]. 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 [149–151]. The role of pulse oximetry in detecting pneumonia is unclear [152,153], and although the chest radiograph is often believed to be the

gold standard, there is variability in the interpretation of radiographs even by pediatric radiologists [154]. Radiographic findings cannot be used to distinguish reliably between bacterial and nonbacterial causes [155,156]. In one South African study, chest radiographs did not affect the clinical outcome in children meeting the World Health Organization definition of pneumonia [157].

Some cases of pneumonia are likely to be clinically occult. Bachur and colleagues [158] found that 19% to 26% of children younger than 5 years old who had a temperature of $\geq$39.0°C, a WBC count $\geq$20,000/mm^3, and no other source or only a "minor" bacterial source on examination had a pneumonia infection as seen on a chest radiograph. A clinical policy by the American College of Emergency Physicians states that a chest radiograph should be considered in children older than 3 months who have a temperature $\geq$39°C and a WBC count $\geq$20,000/mm^3 and that a chest radiograph is usually not indicated in febrile children older than 3 months who have a temperature $\leq$39°C without clinical evidence of acute pulmonary disease [90]. 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°C caused by an unclear source of infection [159]. These recommendations may change based on the decline of the prevalence of pneumococcal pneumonia [160]. 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 [159].

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 has already seems to have had some impact on the practice patterns of pediatricians. Pediatricians who were surveyed were found to order 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 compared with a nonimmunized child [161]. Some authors have begun advocating a less aggressive approach to the evaluation of the immunized febrile child, given the decline in invasive pneumococcal disease with PCV7 [131,133]. Other investigators, however, are urging caution before changing evaluation and management strategies, postulating that invasive pneumococcal disease will persist for several reasons: not all serotypes are covered by vaccine, some children will not be able to mount an adequate immune response to form protective antibodies, and some children still will be incompletely immunized [162].

Other questions regarding PCV7 have arisen. Among the seven serotypes, the amount of disease reduction is variable [34–36]. Furthermore, although the overall rate of invasive pneumococcal disease is lower, there is an increase in the percentage of invasive pneumococcal disease caused by nonvaccine serogroups [33–36]. The clinical implications of this serotype replacement remains unclear but will depend on the capacity of the PCV7 vaccine to protect against these noncovered serotypes as well as the virulence of the nonvaccine strains. Pneumococcal conjugate vaccines intended to cover nine and 11 serotypes are in development [163]. Another question that remains unanswered is the duration of protection afforded to patients who are immunized. Finally, the approach to the patient who is not fully immunized is still unclear. Partial immunization likely provides some protection against pneumococcus; the majority of patients in the post-surveillance PCV7 studies were not fully immunized (ie, three vaccinations), but there was still a decline in invasive pneumococcal disease [33].

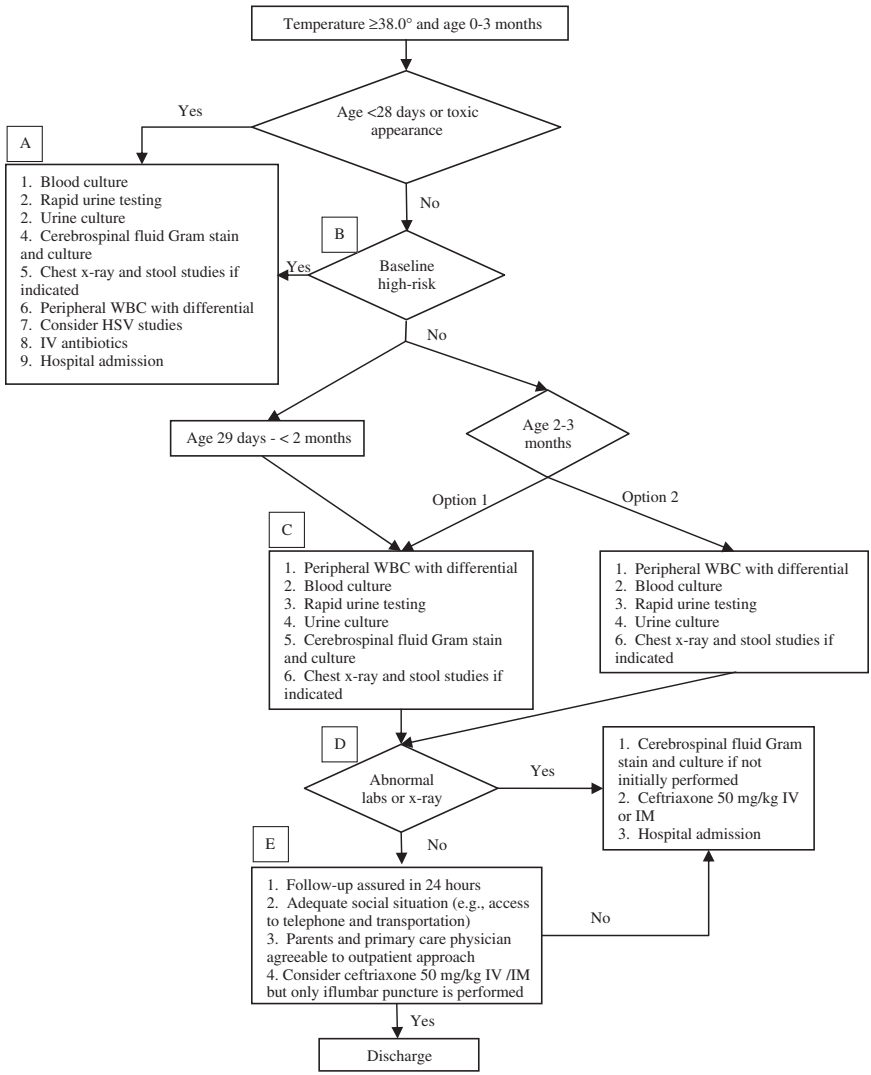
Despite the use of the PCV7 vaccine, patients will still develop bacteremia, and there will be still be a need for better tests to diagnose invasive bacterial disease. Several additional tests are being studied as potential surrogate markers for bacterial disease in young children: procalcitonin (not yet available in the United States), C-reactive protein, and interleukin-6 [164–171].

Summary

Most children 0 to 36 months of age who have fever without an obvious source 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 entails a complete blood count with differential, blood culture, urinalysis and urine culture, lumbar puncture with cerebrospinal fluid analysis, Gram stain and culture, and, when indicated, chest radiographs and stool studies. These patients should receive broad-spectrum parenteral antibiotics before hospital admission. The febrile neonate (0–28 days old) is at high risk for serious bacterial infection, even with 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 cerebrospinal fluid 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 IV, or 100 mg/kg if meningitis is suspected) and cefotaxime (50 mg/kg IV, or 100 mg/kg if meningitis is suspected) or gentamicin (2.5 mg/kg IV).

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 cerebrospinal fluid analysis, Gram stain, and culture should be strongly considered because laboratory

tests such as the white blood cell count are inaccurate in predicting which patients have meningitis. When they are clinically indicated, chest radiographs and stool studies should be obtained as well. If any of these test findings are abnormal (including peripheral WBC $\geq 15{,}000/mm^3$ or $\leq 5000/mm^3$, band-to-neutrophil ratio ≥ 0.2, a urine dipstick test positive for nitrite or leukocyte esterase, or ≥ 5 WBCs/hpf, or organisms seen on Gram stain; cerebrospinal fluid with ≥ 8 WBC/mm^3 or organisms on Gram stain; or ≥ 5 WBC/hpf on the stool specimen or evidence of pneumonia on a chest radiograph), these patients should receive ceftriaxone (50 mg/kg IV or IM, or 100 mg/kg IV if meningitis is suspected)



and should be admitted to the hospital. If these initial laboratory results are normal, a patient can be discharged if follow-up within 24 hours (or sooner if clinically worse) can be assured. The administration of ceftriaxone, 50 mg/kg IV or IM, should be considered if a lumbar puncture is performed, but 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 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 $\geq 39.0^{\circ}C$ 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 two or more of the following risk factors are present: age less than 12 months old, fever for 2 or more days, temperature $\geq 39.0^{\circ}C$, white, and no alternative source of fever. All boys younger than 6 months old and all uncircumcised boys younger than 12 months old should also have catheterized urine sent for rapid urine testing and culture. Based on pre-PCV7 data, the most cost-effective approach to the child who has not had at least three PCV7 doses is to obtain a CBC. If the WBC count is $\geq 15{,}000/mm^3$, a blood culture should be ordered and the administration of ceftriaxone should be considered. Other options (eg, blood culture only or CBC and blood culture with selective antibiotic administration) are reasonable. However, in nontoxic children who have had three PCV7 immunizations and who are not at risk for meningococcal disease, some practitioners believe that obtaining any blood work is unnecessary. The current

Fig. 1. (*A*) Urine testing can be accomplished either by microscopy, Gram stain, or urine dipstick. Chest radiographs are indicated in patients with hypoxia, tachypnea, abnormal lung sounds, or respiratory distress. Stool studies are indicated in patients with diarrhea. Herpes simplex virus 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 IV, or 100 mg/kg IV if meningitis is suspected) and cefotaxime (50 mg/kg, or 100 mg/kg IV if meningitis is suspected) or gentamicin (2.5 mg/kg IV). Additionally, neonates with findings suggestive of HSV infection should receive acyclovir (20 mg/kg IV). Older children should receive ceftriaxone (50 mg/kg IV, or 100 mg/kg IV if meningitis is suspected). A WBC count with differential may be ordered, but the results should not dissuade the clinician from pursuing a full evaluation and treatment with antibiotics. (*B*) Young patients who have increased underlying risk include children who were premature, had prolonged hospital stays after birth, those with underlying medical conditions, patients with indwelling medical devices, fever lasting longer than 5 days, or patients already on antibiotics. (*C*) Urine testing can be accomplished either by microscopy, Gram stain, or urine dipstick. Chest radiographs are indicated in patients with hypoxia, tachypnea, abnormal lung sounds, or respiratory distress. Stool studies are indicated in patients with diarrhea. (*D*) Abnormal laboratory findings: peripheral WBC count $\leq 5{,}000/mm^3$ or $\geq 15{,}000/mm^3$ or band-to-neutrophil ratio ≥ 0.2; urine testing, ≥ 5 WBC/hpf, bacteria on Gram stain, or positive leukocyte esterase or nitrite; cerebrospinal fluid, ≥ 8 WBC/mm^3 or bacteria on Gram stain; stool specimen, ≥ 5 WBC/hpf; and chest radiograph, infiltrate detected. (*E*) Administering ceftriaxone (50 mg/kg IV or IM) is optional but should only be considered in patients who have undergone lumbar puncture. Patients who have not undergone lumbar puncture should not get ceftriaxone. (*Adapted from* Baraff L. Management of fever without source in infants and children. Ann Emerg Med 2000;36(6):602–14.)

evidence suggests that this may become a reasonable approach, but studies addressing this specific approach have not yet been published (Figs. 1 and 2).

Finally, it is critically important to recognize that there is no combination of clinical assessment and diagnostic testing that will successfully identify all patients with serious infection at the time of initial presentation. Therefore, the importance of timely reassessment cannot be overemphasized, and caretakers must be instructed to return to the ED or the office immediately for any deterioration in the child's condition. While strategies such as that described above may help guide the evaluation and treament of febrile young infants,

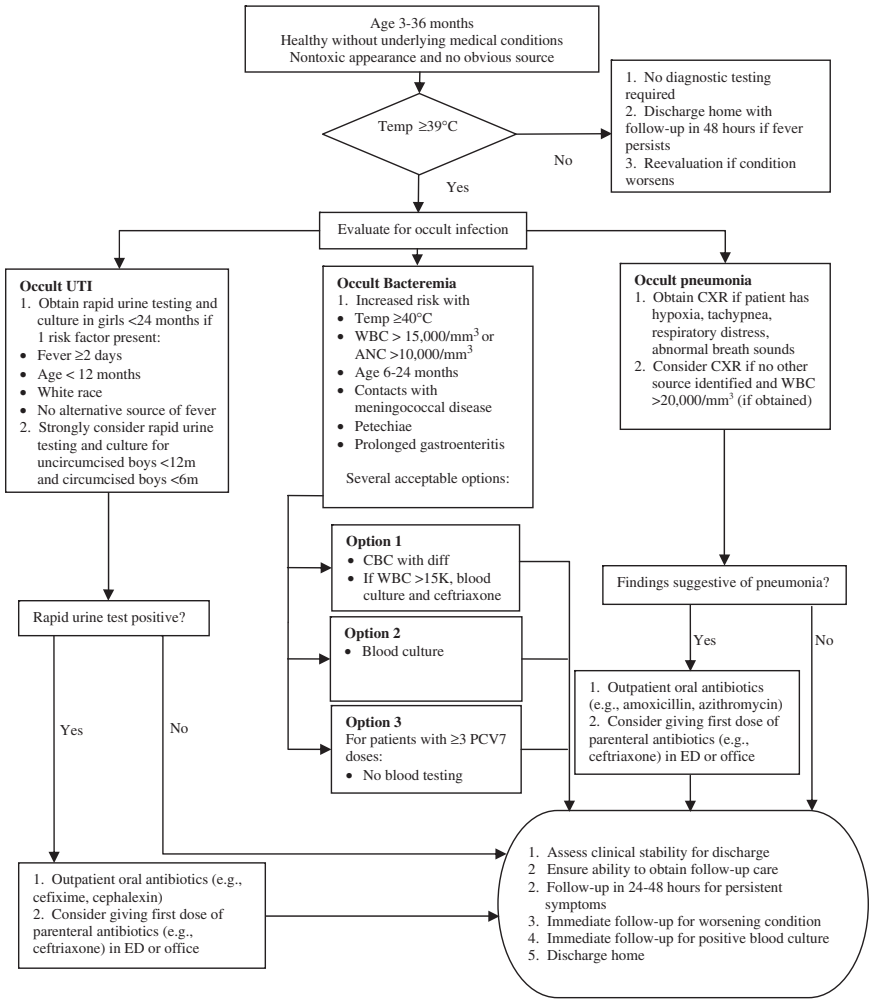


Fig. 2. Algorithm for treating children aged 3 to 36 months old (may be used for patients 2 to 3 months old as well; see text). (*Adapted from* Baraff L. Management of fever without source in infants and children. Ann Emerg Med 2000;36(6):602–14.)

no single approach can capture the nuances of all febrile young patients. Therefore, this approach should serve as an adjunct to, and not a replacement for clinician judgment.

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