

# PEDIATRIC EMERGENCY MEDICINE PRACTICE

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## Fever Caused By Occult Infections In The 3-To-36-Month-Old Child

*It's 3 am and the ED is winding down. You look up to find that the next patient to be seen is a 9-month-old with the chief complaint of "fever." You swig down the last of your lukewarm coffee, grab the chart, and head off to room 5.*

*On entering, you find a teary-eyed white female infant sitting in her mother's lap, eyeing you suspiciously. Mom relates that she has been ill for the past three days with upper respiratory congestion and a nonproductive cough, which her mom has been treating with an over-the-counter decongestant. Today, however, the child was less active, drank less of her formula than usual, and felt hot to the touch, prompting Mom to check her temperature. Her initial fever of 101.2°F responded to a dose of acetaminophen, but when the mother rechecked the child's temperature several hours later, it had climbed to 103.5°F, so she called her pediatrician's answering service and was told to bring her immediately to the emergency department.*

*The young girl has had two episodes of nonbloody, nonbilious emesis related to her cough, no diarrhea or rash, and has maintained her urinary output. She has been exposed to other children with upper respiratory illnesses in her day care class. To date, however, she has been in good health—no underlying medical conditions and no chronic medications or allergies, and her immunizations are current. When seen in triage 30 minutes ago, she was given another dose of acetaminophen by your nursing staff.*

*Your examination reveals an alert but quiet patient who is nontoxic-appearing and apparently well hydrated. She reaches for your stethoscope while drinking from her bottle. With examination, she gets appropriately cranky but calms easily with her mother's touch. No source for her fever is readily identifiable—her tympanic membranes are normal in appearance, her chest is clear, she has no rash, and her physical findings are reassuring.*

*Mom is concerned about several issues: the height of the fever, the fact that it*

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### Author

**Timothy G. Givens, MD**

Associate Professor of Emergency Medicine & Pediatrics, Vanderbilt University Medical Center, Nashville, TN

### Peer Reviewers

**Jeffrey Avner, MD**

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**Andrew DePiero, MD**

Attending Physician, Division of Emergency Medicine Alfred I. duPont Hospital for Children, Wilmington, DE; Assistant Professor of Pediatrics, Jefferson Medical College, Philadelphia, PA

**Martin L. Herman, MD, FAAP, FACEP**

Professor of Pediatrics, Division of Critical Care and Emergency Services, UT Health Sciences School of Medicine, Cordova, TN

### CME Objectives

Upon completing this article, you should be able to:

1. Review and critically appraise existing practice guidelines for treating fever without a source in 3- to 36-month-old children in light of recent medical literature.
2. Understand the changing epidemiology of occult infection in young children due to widespread immunization and the implications in testing for and treating occult infection.
3. Review the diagnostic tests available for identifying children at risk for occult infection and understand their utility and limitations.
4. Consider the increasing importance of occult urinary infection in young children and the clinical conditions that place them at greater risk.

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### Research Editor

**Christopher Strother, MD**

Fellow, Pediatric Emergency Medicine, Mt. Sinai School of Medicine; Chair, AAP Section on Residents, New York, NY

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didn't go away with an antipyretic dose, and the possibility of seizures or worse—"brain damage"—due to the high fever. She expects that you will check a blood count—her pediatrician usually does—and prescribe an antibiotic. A number of thoughts run through your head as you consider how to proceed:

- What is the patient's risk of occult infection?
- Are there any laboratory investigations that will guide your decision to treat (or not to treat) her with an antibiotic?
- Does the patient's immunization status affect your approach?

**F**ever is a common presenting complaint among pediatric patients, accounting for approximately 20% of emergency department (ED) visits by children.<sup>1,2</sup> Hence, management of the febrile child is a challenge faced by emergency physicians on a daily basis. Despite the fact that the vast majority of children with fever have self-limited viral illnesses,<sup>3</sup> there is a finite number who may harbor serious bacterial illnesses (SBIs), and, in many cases, these patients are clinically indistinguishable from the rest. The emergency physician's challenge is to identify and treat those children who have SBIs while avoiding overtreatment with antibiotics of those without SBIs, thereby limiting the propagation of antimicrobial resistance. Making this distinction is particularly difficult early in the course of a febrile illness. In addition, this decision process is often conducted in the setting of a family with "fever phobia." Many myths regarding fever exist among the general public, and these misconceptions are often reinforced by the mixed messages that we in the medical community provide. Assessing the risk of SBI to an individual patient, selectively making reasonable diagnostic and therapeutic interventions, and simultaneously reassuring and educating families regarding appropriate concern for fever can make what appears to be a routine common complaint an important and challenging encounter.

Some instances of fever in children require simple decision making. When a child with fever has an evident source of infection, such as acute otitis media or acute gastroenteritis, decisions are relatively straightforward: treat the source and manage the patient's condition appropriately. In the case of the febrile patient with an underlying medical condition (such as sickle-cell disease) or indwelling hardware (such as a central venous catheter), diagnostic investigations and empiric therapy are usually protocol-driven. These circumstances place the patient at greater risk for SBI, and more aggressive management is apropos. This conservative approach extends to the youngest infants (less than 2-3 months of age), who have yet to develop a fully competent

immune response. Finally, any patient who appears "toxic" demands a comprehensive search for the source of fever and empiric broad-spectrum antibiotic coverage until the clinical picture clears. This is true whether the patient is 45 days or 45 years of age.

Like the child in our vignette, however, it is the febrile pediatric patient without a readily identifiable source of infection, an unremarkable medical history, and a nontoxic appearance who can be the most challenging. What is this patient's risk of SBI? Are there laboratory tests that can guide us in pinpointing those at risk? Who should receive antibiotics? And what is an appropriate disposition and follow-up plan for these patients?

### Critical Appraisal Of The Literature

The story of occult infection in children is an evolving one, and practice has changed over the past 30 years. Much of the initial literature regarding fever in the 3-year-and-under age group focused primarily on the identification of clinically inapparent infection in the form of "occult bacteremia" and the effort to prevent the potentially serious sequelae of bacteremia, such as meningitis, osteomyelitis, or pneumonia. Early investigations predated the availability of broad-spectrum parenteral antibiotics such as ceftriaxone, technology enabling continuous monitoring and detection of microorganisms in culture media, and development and widespread implementation of immunizations against the more common pathogens. As the landscape of occult infection in children has changed, more recent literature has attempted to take these factors into account, modifying recommendations and expanding the focus to include newer resistant organisms and the identification of other "occult" infections, such as urinary tract infection (UTI) or pneumonia.

Many ED physicians predicate their approach to febrile children on the practice guidelines outlined in a landmark 1993 article that appeared simultaneously in both *Pediatrics* and the *Annals of Emergency Medicine*. Because of their prominent display in the journals published by the American Academy of Pediatrics and the American College of Emergency Physicians, these guidelines had a certain voice of authority and quickly became a de facto standard of practice. A panel of experts chosen by the primary author performed a review of the existing literature at that time and arrived at recommendations on how to approach children of various ages with fever.

These guidelines included two recommended options in the pursuit of occult bacteremia for children 3 to 36 months of age with a fever of 39°C (102.2°F) or greater without an identifiable source of infection: 1) obtain a blood culture and administer empiric treatment with parenteral antibiotics (ceftriaxone) pending culture results in *all* children meeting the above criteria; or 2) selectively culture and treat those whose white blood cell count (WBC) exceeds 15,000 muL. In addition, urine culture obtained by catheterization or suprapubic aspiration was recommended for all boys less than 6 months of age and all girls younger than 24 months.<sup>4-5</sup>

Historically, much of the medical literature that laid the groundwork for this approach to occult infection in children originated in the 1970s and '80s and was a patchwork of sometimes flawed and inconsistent data. Initial reports simply described bacteremia rates as they varied by patient age and height of fever and characterized the primary offending organisms in a variety of population samples.<sup>6-19</sup> Most were gathered from patients seen in emergency departments and outpatient clinics, not in private practitioners' offices, a fact that injected a healthy dose of selection bias. None of the studies that applied a temperature threshold for initiating a fever workup accounted for prior use of antipyretics or subjective parental reports of fever in assessing bacteremia risk. Thus initial estimates of occult bacteremia rates in children less than 36 months of age were likely overstated and did not represent true prevalence data.<sup>20-22</sup> Nonetheless, they laid the groundwork for subsequent efforts to find and stop bacteremia in its tracks.

Furthermore, the 1993 guidelines are the result of a meta-analysis of existing studies, so they are only as good as the studies upon which they are based. The inclusion criteria (age, height of fever, etc.), the laboratory tests performed, the degree of WBC elevation associated with bacteremia, and the use of empiric antibiotics varied from study to study, making comparative analysis problematic. Some investigations lumped patients who had an identifiable source of infection (such as otitis media or pneumonia) with those without an apparent source on exam, which inevitably confounds interpretation of the results. Patients with a presumed bacterial source of infection would be expected to have a greater rate of bacteremia, and they would likely receive antibiotic therapy regardless of their WBC. In fact, because most of these studies did not *randomly* treat or not

treat children with antibiotics, the group of children who were treated often already had one of the outcomes of interest and thus had a lower probability of *subsequently* developing a new focus of infection, biasing the outcomes of these studies in favor of antibiotic treatment.<sup>23</sup>

The other presumption of the guidelines is that therapy with antibiotics (oral or parenteral) is effective in preventing sequelae, particularly meningitis, and it is not clear that this has been proven.<sup>24-33</sup> After the guidelines appeared, editorials written by prominent pediatric infectious disease specialists warned against the blanket use of ceftriaxone as a panacea.<sup>23,34-36</sup> In some of the studies promoting expectant antibiotic treatment, for example, recommendations were based upon the outcomes of the subset of patients with positive blood cultures and not the population of febrile children *at risk* for bacteremia as a whole. Naturally, few would quibble about treating patients with demonstrated bacteremia; but the issue—particularly for the emergency physician—remains to reliably identify which patients have bacteremia and selectively treating those. Even in the best case scenario, blood culture results are not available for 12-24 hours after they are obtained and are, therefore, not helpful in front-end decision making. To date, no readily available laboratory test(s), including the WBC, has been discovered that consistently and accurately positively predicts the presence of bacteremia. So, for the physician confronting the child with fever in real time, the question remains: who, if anyone, do you treat expectantly?

After the 1993 guidelines appeared, several surveys of the practicing medical community were circulated to assess their impact. It rapidly became clear that many emergency physicians were either unaware of the guidelines or actively chose not to follow them.<sup>37-38</sup> This was true not only for pediatric emergency physicians, but for general emergency physicians and primary care practitioners as well.<sup>39-40</sup> Further, those who were aware of and invoked the guidelines did not always apply them consistently.<sup>41</sup> The use of ceftriaxone became widespread, in many instances indiscriminate and not in accordance with the published guidelines—the proverbial hammer for every nail that presented itself. This may have stemmed from the option, suggested by the 1993 guidelines, to treat everyone at risk (i.e., with a fever greater than 102.2°F without an obvious source). But many physicians obtained screening laboratories on

patients, disregarded the (normal) results, and administered ceftriaxone anyway. While this strategy may provide an immediate sense of security for the emergency physician, who may feel that s/he has limited his or her personal liability and protected the patient in giving ceftriaxone, s/he may simultaneously be tying the hands of his or her partners in primary care and painting us all into the corner of antibiotic resistance in the long run. As was pointed out by early critics of ceftriaxone use in the emergency department, once this long-acting, broad-spectrum, blood-brain barrier-crossing antibiotic has been administered, the parents and the primary care physician providing follow-up evaluation are robbed of their abilities to assess the child's clinical condition or need for continuing therapy.<sup>34-35</sup> And even if we grant that one or two doses of parenteral ceftriaxone are effective in treating bacteremia, two doses of ceftriaxone would be inadequate to treat meningitis if the child had already seeded the meninges. Clearly there is no easy or right answer to the question, to treat or not to treat?

Complicating the picture is the falling prevalence of SBIs as immunizations against the more common offending organisms—*Haemophilus influenzae* type B (HIB) and *Streptococcus pneumoniae*—have been developed and implemented on a widespread basis.<sup>42-44</sup> As rates of bacteremia and invasive infections due to these agents decline and, concomitantly, as the levels of resistance to our current antibiotics rise (witness the prolific emergence of MRSA and drug-resistant *S. pneumoniae*), management strategies we learned during our training years have become outdated and may no longer apply. The landscape of fever in children is constantly evolving, and the emergency physician must adapt his or her approach accordingly. This is not always easy, as old habits die hard. A recent study by Cox et al. highlighted that physicians tend to adhere to published guidelines or algorithms they were exposed to during their residency training, despite the appearance of newer or contradictory findings in the medical literature.<sup>45</sup> Though it is difficult to reconsider what was once dispensed as gospel, it is incumbent upon practicing physicians to modify their approach to the febrile child as new data and therapies emerge.

Fortunately, the guidelines have been appropriately revisited and modified to reflect the current situation.<sup>46-52</sup> While some current investigators persist in the attempt to build a better mousetrap for predicting SBI than the WBC (the absolute neutrophil

count [ANC], C-reactive protein [CRP], and various cytokines have been posited as more appropriate substitutes),<sup>53-62</sup> these newer laboratory indices are rapidly becoming weapons in search of a war. Vaccination effectiveness has led several commentators to suggest that the search for occult bacteremia may already have become the medical equivalent of tilting at windmills.<sup>48,50-51</sup> Hence, the emphasis in more recent literature on fever in this 3-to-36-month age group is on detecting other sources of occult infection, such as UTI.<sup>63-69</sup>

## **Epidemiology, Etiology, And Pathophysiology**

Fever strikes fear into the hearts of parents—and clinicians as well. While we recognize it as a physiologic response in infection or inflammation, with many beneficial effects,<sup>70</sup> fever also makes patients feel crummy and often look worse. It increases the metabolic rate and tissue demands, bringing tachypnea, tachycardia, and sometimes diaphoresis and chills. But fever is merely a symptom—a highly important and helpful symptom—and *not* a disease. Families do not commonly understand this distinction, as fever is what they can see and feel and measure with a thermometer (if they have one). They often misunderstand the role of antipyretic medications and their pharmacokinetics and the fact that when antipyretics are metabolized (i.e., wear off) because the physiologic set point (i.e., thermostat) has been reset, the fever will generally return for as long as the inciting illness persists. While fever usually signals infection, and higher fevers can represent more serious infection, this is not always the case. Severity of illness and height of fever are not often closely correlated—some benign viral illnesses can produce temperatures in excess of 40°C, while sepsis and meningitis may present with normal temperatures or even hypothermia.<sup>71</sup> It is the presence or absence of fever that matters, not the height of the fever.<sup>72</sup> Accordingly, fever must be put into clinical context with the child's circumstances and overall appearance in order to frame a rational approach to determining its etiology.

When a child appears “toxic,” a comprehensive search for the fever source is indicated, as alluded to in the introduction. This is true regardless of the degree of fever. Presumptive antibiotic therapy usually follows hand in hand with this schema. However, in the well-appearing, nontoxic child there is a small but finite chance of serious bacterial illness

that gives no outward clues to its existence—hence the term “occult.” Are there patterns or trends that may give the clinician clues to the existence of SBI in any given patient? Multiple studies have made valiant attempts to get their arms around this elusive subject.

### Occult Bacteremia

At what threshold of temperature elevation is bacteremia likely? The earliest descriptive studies (circa 1970s) of bacteremia in pediatric outpatients correlated an increasing rate of bacteremia with an increasing degree of temperature elevation. At a core temperature of 100.5°F (38.0°C), blood cultures yielded positive results less than 1% of the time, but cultures obtained in children with fever of 102.2°F (39.0°C) were positive in 3%-11% (mean = 4.3%) of cases, and at 104°F (40.0°C), the yield increased to 4%-17%.<sup>7-8,15-16</sup> Again, not all the patients included in these studies had fever without an apparent source of infection. Note, too, that even at 104°F, 80% or more of patients did not have a bacterial pathogen isolated from the bloodstream. Nonetheless, based on these data, the consensus of those advocating laboratory investigation of fever without source settled on 102.2°F or a positive blood culture yield in the neighborhood of 5% as a justifiable threshold for screening.

But is it? Is bacteremia per se the therapeutic target? What are the consequences (i.e., what is the *natural history*) of undiagnosed occult bacteremia? To answer this question, we must know which are the most common organisms causing bacteremia in this age group and how they behave. Initial studies from the pre-vaccine era found that, while other organisms were occasionally responsible for occult infection, three were overwhelmingly the primary culprits: *S. pneumoniae*, HIB, and *Neisseria meningitidis*.<sup>7-8,11,15-19</sup> *S. pneumoniae* was consistently the most prevalent organism, accounting in early reports for upwards of 80% of bacteremia cases. It also is historically associated with a relatively low incidence of infectious sequelae. In fact, in untreated patients who grew *S. pneumoniae* from a blood culture obtained for fever, more than 90% were afebrile and had spontaneously cleared their bacteremia when reexamined and recultured. Those who remained persistently bacteremic generally had a low rate of invasive disease and responded well to antibiotic therapy initiated only after a positive culture result, without untoward outcomes.<sup>7-8,43</sup>

*H. influenzae* type B, a highly invasive organism,

is a different story altogether. Patients with HIB bacteremia develop focal complications (especially meningitis) in about a third of cases,<sup>73-74</sup> and empiric antibiotic treatment has been posited to reduce the incidence of sequelae from HIB.<sup>29</sup> It is precisely this kind of bacteremia that drove the development of protocols and guidelines for fever workups, as detection and treatment of early HIB disease could exert a tangible effect on outcome. Fortunately, cases of invasive HIB disease have fallen precipitously since implementation of the conjugate vaccination against it, making concern for HIB almost a moot point at this juncture.<sup>43,75-76</sup> Residents in training today approach *H. influenzae* disease as a historical footnote, much as those of us who trained in the 1970s and '80s view poliovirus.

The possibility of occult meningococcal bacteremia has always been a fearful one, as the disease can run a fulminant course and produce devastating results. But *N. meningitidis* occurs sporadically in epidemic and endemic clusters, and the numbers of published cases are generally too small to make meaningful or significant conclusions. One 10-year series of meningococemia, for example, included only 25 cases,<sup>77</sup> of which 12 were unsuspected (the others presented with shock, purpura fulminans, or the like—not exactly occult disease). However, 8 of these remaining 12 had a source of infection on examination (otitis or pneumonia), received antibiotics, and recovered without sequelae. Patients with meningococcal bacteremia who receive empiric antibiotics tend to fare better than those who do not, and one would certainly recommend antibiotics for these patients if one knew who they were. But the crux of the discussion still turns on whether we can reliably find the needle (the bacteremic child) in the haystack<sup>47</sup> of all nontoxic-appearing febrile children, whatever the organism.

The widespread introduction of a conjugate vaccine against HIB was followed by a decline in the overall prevalence in the 3-to-36-month age group of occult bacteremia from all pathogens to less than 2%.<sup>43,75</sup> Post-HIB surveillance data indicate a near-complete disappearance of HIB disease<sup>75,78-79</sup> and a decline in overall prevalence of bacteremia, resulting in *S. pneumoniae* accounting for greater than 90% of remaining cases of bacteremia. Among children with untreated pneumococcal bacteremia, a small number (approximately 3%-5%, though this figure is controversial) have the potential to develop pneumococcal meningitis or other severe complications,<sup>11,30,32,80-81</sup> so

recommendations persist for screening and selective treatment of young febrile children at high risk with empiric antibiotic therapy.

Since the release and widespread use of a vaccination against the seven most common antigenic serotypes of *S. pneumoniae* (PCV7), which are known to account for greater than 80% of pneumococcal disease, cases of pneumococcal bacteremia have also fallen. The most recent investigations document an occult bacteremia rate of 1%-2% or less,<sup>43,75</sup> making a blood culture obtained in the ED setting at least as likely to produce a contaminant as a true pathogen. Several theoretical models, or decision analyses, have been published pertaining to occult bacteremia in an attempt to discern the most efficient and cost-effective strategy against it, given prevailing conditions.<sup>25,82-84</sup> The most recent of these (2001) cites a bacteremia rate of 0.5% as the cutoff point where empiric testing and treatment should cease.<sup>84</sup> The investigators suggest that, at current estimated bacteremia rates, the strategy "CBC + selective blood culture and treatment" is still more cost-effective than "no workup." However, surveillance data necessarily lags a bit behind the institution of an intervention such as immunization, and if we are not at the 0.5% threshold today, we are very close. Stay tuned.

### Occult Urinary Tract Infection (UTI)

At the same time that the pursuit of occult bacteremia is becoming passé, an increased awareness of the importance of finding and treating UTI in children has developed. Though long-term follow-up data are lacking, there have been reports that UTI in childhood may be associated with development of hypertension or end-stage renal disease in adulthood.<sup>85</sup> Specific symptoms for UTI (such as dysuria, frequency, urgency, or flank pain) are commonly absent or are, at best, difficult to elicit in the child under the age of 2-3 years who is still wearing diapers and not yet potty trained. Although nonspecific symptoms, such as poor feeding, vomiting, or irritability, may herald a urinary tract infection, it is often fever alone that is the only clue to the presence of a UTI in young children.<sup>64-65,67,69</sup> It has widely been held that the presence of fever in the setting of UTI is prima facie evidence of upper urinary tract disease (i.e., pyelonephritis).<sup>69</sup> In fact, nuclear scanning techniques, such as DMSA scans, have demonstrated evidence of pyelonephritis in 34%-70% of children with UTI and fever.<sup>86-88</sup>

The population we are concerned with—nontox-

ic-appearing children under 36 months with fever and no apparent source on examination—have been reported in two fairly large recent studies to have a prevalence of UTI of 3.5%-5.5%.<sup>63,65</sup> While girls are about twice as likely as boys to have a UTI, uncircumcised boys have an eightfold increased risk over circumcised boys. Curiously, both of these large prevalence studies found a rate of UTI in Caucasian girls as high as 16%-17%. Why this is so is not known. Although both studies were conducted in emergency departments and may contain an element of referral bias, there are suggested pathophysiologic factors (lack of secretion of carbohydrates that prevent bacterial adhesion in the urinary tract) that may predispose Caucasian girls to this phenomenon.<sup>89-90</sup>

The authors of one of these prevalence studies next developed a decision rule to assist in pinpointing specifically which febrile girls less than 2 years of age should have their urine cultured in an effort to detect UTI. They identified five independent variables: age less than 12 months, white race, temperature greater than 39°C, fever for two or more days, and absence of any other source of fever on physical examination. In their analysis, the presence of two or more of these five variables predicted UTI with a sensitivity of 0.95 (95% CI, 0.85-0.99) and a specificity of 0.31 (95% CI, 0.28-0.34). In their study population, in which the overall prevalence of UTI was 4.3%, the positive predictive value (PPV) of the presence of two or more variables was 6.4%, and the negative predictive value of the presence of fewer than two variables was exceedingly high. Translated, this implies that obtaining urine specimens on only those girls less than 2 years of age with two or more identified risk factors would have identified more than 95% of all UTIs while eliminating 30% of unnecessary cultures.<sup>66</sup> This decision rule was subsequently validated retrospectively in a case-control study in an independent sample of girls less than 2 years of age from a different pediatric emergency department. The later study found, however, that sensitivity and specificity of the decision rule were better using a threshold of three or more of the predictive factors.<sup>68</sup>

### Occult Pneumonia

The most common cause of pneumonia in young children 3 to 36 months of age is viral disease. Prior to the institution of pneumococcal vaccination, *S. pneumoniae* was the prevailing bacterial cause of pneumonia in this age group (and may still be).<sup>91</sup>

Clinical diagnosis of pneumonia is fraught with error, and although clinical decision rules highlighting physical examination findings (such as tachypnea, asymmetric breath sounds, and rales or crackles) have been elaborated none has been successfully validated.<sup>92-94</sup> Whether hypoxemia measured by pulse oximeter is helpful in elucidating pneumonia is not clear.<sup>95</sup> In the past, the chest radiograph has been held to be the gold standard for diagnosis of pneumonia, though radiographic findings cannot reliably distinguish between viral and bacterial disease,<sup>96-97</sup> and there is considerable variation in radiographic interpretation of chest films, even among pediatric radiologists.<sup>98</sup> Suffice it to say that confidence in distinguishing bacterial pneumonia in children is elusive. Ongoing efforts to use more sophisticated diagnostic techniques, such as polymerase chain reaction (PCR) based assays, may augment this ability in the future. For the time being, it looks like we're stuck with "atelectasis versus infiltrate" and knowing that many of the infiltrates we're treating with antibiotics may represent viral disease.

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## Differential Diagnosis

The differential diagnosis of fever in the 3-to-36-month-old child is broad and includes infections, malignancy, rheumatologic conditions, toxic ingestions, and environmental causes. For the purposes of this discussion, we have confined ourselves to nontoxic-appearing children without major comorbid conditions who have no apparent source for their fever on examination. Far and away, infections predominate in this age group, and the vast majority of those are viral in origin. There is a finite number of these patients who have an underlying SBI—typically bacteremia, urinary tract infection, or pneumonia. We have focused our efforts on the identification of children with these three diagnostic entities.

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## Prehospital Care

The role of the emergency medical services (EMS) provider in the care of a child with fever is fairly straightforward: address the adequacy of airway, breathing, and circulation; assess the patient for problems associated with fever that may require emergency treatment, such as wheezing or dehydration; and transport the child to an appropriate care facility. Many state EMS protocols do not specifically address fever in children as a separate entity. Those

that do appropriately counsel that fever in and of itself is not the problem and that EMS personnel should limit their interventions. Submersion of patients in water and direct application of either ice or rubbing alcohol are discouraged. It is generally not within the purview of the EMS provider to determine a source of the fever but rather to ensure physiologic stability and safe transport.

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## ED Evaluation

After assuring that the ABCs are intact, the first step in any emergency department evaluation of a febrile child is a thorough history and physical examination. The goal is to screen for those patients who either 1) appear toxic or 2) have an underlying medical condition that might mandate a comprehensive diagnostic approach and empiric broad-spectrum antimicrobial therapy. These patients include those who are immunosuppressed by virtue of their medical condition (sickle-cell disease, nephrotic syndrome, known immunodeficiency state) or an exogenous medical therapy (such as chemotherapy for malignancy or treatment for collagen vascular disease or inflammatory bowel disease). These patients are typically admitted to the hospital pending culture results.

Next, a detailed physical examination searching for an infectious source, such as cellulitis or pneumonia, is undertaken. If a source is identified, appropriate antimicrobial treatment that takes into account prevailing local pathogens, existing allergies, and the individual patient's prior treatment history (for example, recurrent otitis media, refractory to amoxicillin) should be prescribed and timely follow-up arranged.

If the patient is nontoxic-appearing despite the fever, has no underlying risk factors, and has an unrevealing physical examination, the ED physician has reached a decision point: shall I pursue a diagnostic workup in an effort to discover if my patient is at risk of occult SBI? If so, which tests are appropriate?

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## Diagnostic Studies

Much literature has centered on the ability of the white blood cell count (WBC) to predict the presence of bacteremia. How helpful is the WBC in accomplishing this end? The 1993 guidelines established a standard of WBC greater than or equal to

15,000 muL as the threshold for the initiation of empiric antibiotic therapy.<sup>4,5</sup> The literature supports the idea that this standard is a fair predictor of pneumococcal bacteremia: more than 75% of patients with *S. pneumoniae* in the bloodstream will have a WBC of 15,000 muL or more. (Recall here that more than 90% of pneumococcal bacteremia clears spontaneously without treatment and that there is a naturally low rate of invasive pneumococcal disease). However, a WBC of 15,000 muL or more is present in fewer than 50% of patients with HIB bacteremia and in fewer than 30% of patients with meningococcal bacteremia.<sup>17,74,77</sup> Further, the vast majority of febrile patients with a WBC of 15,000 muL or more are NOT bacteremic.<sup>23</sup> In fact, the positive predictive value (PPV, or percentage of positive test results that indicate actual presence of disease) of a WBC of 15,000 muL or more is 75% for *viral* infection.<sup>3</sup> In studies that examined the positive predictive value of a WBC greater than 15,000 muL for all types of bacteremia, the PPV ranged from 3.4% to a high of 21%.<sup>7-8,16-17,99-100</sup> Therefore, because of the relatively low prevalence of disease (bacteremia) in the population at large, WBC is actually an extremely *poor* screening test for predicting bacteremia, and it's getting worse as the rate of bacteremia declines.

In light of the WBC's less-than-stellar performance, other laboratory parameters have been sought as surrogate predictors of bacteremia. An ideal screening test would be inexpensive, quick, readily available in most settings, accurate, and relevant to the question at hand. The absolute neutrophil count (ANC), or absolute total number of granulocytes (polymorphonuclear cells plus band forms), has been evaluated in several studies to date. Kuppermann et al. suggested, based upon 164 cases of occult pneumococcal bacteremia in 6579 patients, that an ANC value of 10,000 muL or more was a better discriminator of bacteremia than a total WBC of 15,000 muL or more.<sup>101</sup> Lee and Harper assessed the risk of bacteremia in the post-HIB era and found no difference between ANC and WBC in terms of ability to predict bacteremia but suggested revising the cutoff value for total WBC to 18,000 muL in order to increase specificity (limit overtreatment with antibiotics) without sacrificing sensitivity.<sup>75</sup> Note that both of these investigations looked at the discriminatory value of these laboratory tests for pneumococcal bacteremia only and not bacteremia in general. Isaacman et al. attempted to rectify this issue by using logistic regression analysis to characterize bac-

teremia risk by assessing age, WBC, polymorphonuclear cell count (PMN), band count, ANC, and temperature. While in their study ANC was a more accurate predictor than WBC or band count alone, it had to be inserted into a complex, unwieldy formula in order to compute an individual patient's risk,<sup>102</sup> not the most conducive approach in the ED setting.

Kuppermann and Walton explored whether the absolute number or the relative percentage of immature neutrophils (band forms) on a peripheral blood smear or the resultant band-neutrophil ratio could be used to more accurately predict bacteremia in febrile children. A prospective study from three pediatric emergency departments showed that, while ANC tended to predict bacterial disease, absolute band count and band-neutrophil ratio were not helpful in discriminating bacterial versus viral disease.<sup>103</sup> This is underpinned by numerous reports from the pathology and clinical laboratory literature that highlight the inconsistency of laboratory technicians and pathologists in discriminating band forms from mature neutrophils.<sup>104-107</sup> The resultant variability and imprecision cast doubt on the band count's clinical utility. Based on this, one recent investigation concluded that quantitative reporting of band cell count should cease.<sup>107</sup>

Several investigators have looked at acute phase reactants, such as C-reactive protein (CRP), as predictors of occult bacteremia. Like WBCs and differential counts, CRP levels are readily available in emergency departments, are relatively quick and inexpensive, and have previously been shown to be helpful in delineating bacterial from viral illness in various patient populations.<sup>57</sup> Pulliam et al. prospectively compared the ability of CRP to predict SBI with that of WBC, ANC, and band count in a convenience sample of 77 patients.<sup>56</sup> Several factors suggest that selection bias was a prominent feature of this study, including the relatively higher rate of SBI (18%), relatively lower mean age, and high rate of patients referred to the ED for evaluation, compared with other studies of occult bacteremia. Nonetheless, the authors found that CRP was superior (had greater sensitivity and specificity) to either WBC or ANC in predicting SBI, particularly at a value of 7 mg/dL or greater. This finding mirrors that of earlier studies that were performed in the pre-HIB vaccine era. In 2002, Isaacman and Burke published an evaluation of the comparable predictive value of CRP vis-à-vis WBC and ANC in a sample of 256 patients with an SBI rate of 11.3% (29 cases—17



pneumonia, 9 UTI, 3 bacteremia).<sup>57</sup> They could not corroborate the findings from Pulliam et al. Using a CRP cutoff value of 7 mg/dL identified only 37% of those with SBI in the Isaacman study, which was deemed an unacceptable level of sensitivity. In fact, Isaacman and Burke found that CRP neither independently nor in combination with either WBC or ANC significantly increased diagnostic accuracy for SBI. One unforeseen finding in the Isaacman study was that cases of bacteremia in their sample had fallen to such a low incidence that it was difficult to continue to recommend performing screening tests of any kind at these levels. In an accompanying editorial, both Isaacman and Burke<sup>57</sup> and Kuppermann<sup>48</sup> speculated that, in light of widespread immunization, it is high time to reconsider our approach to occult bacteremia and focus instead on patient education and clinical follow-up as the cornerstones of fever management.

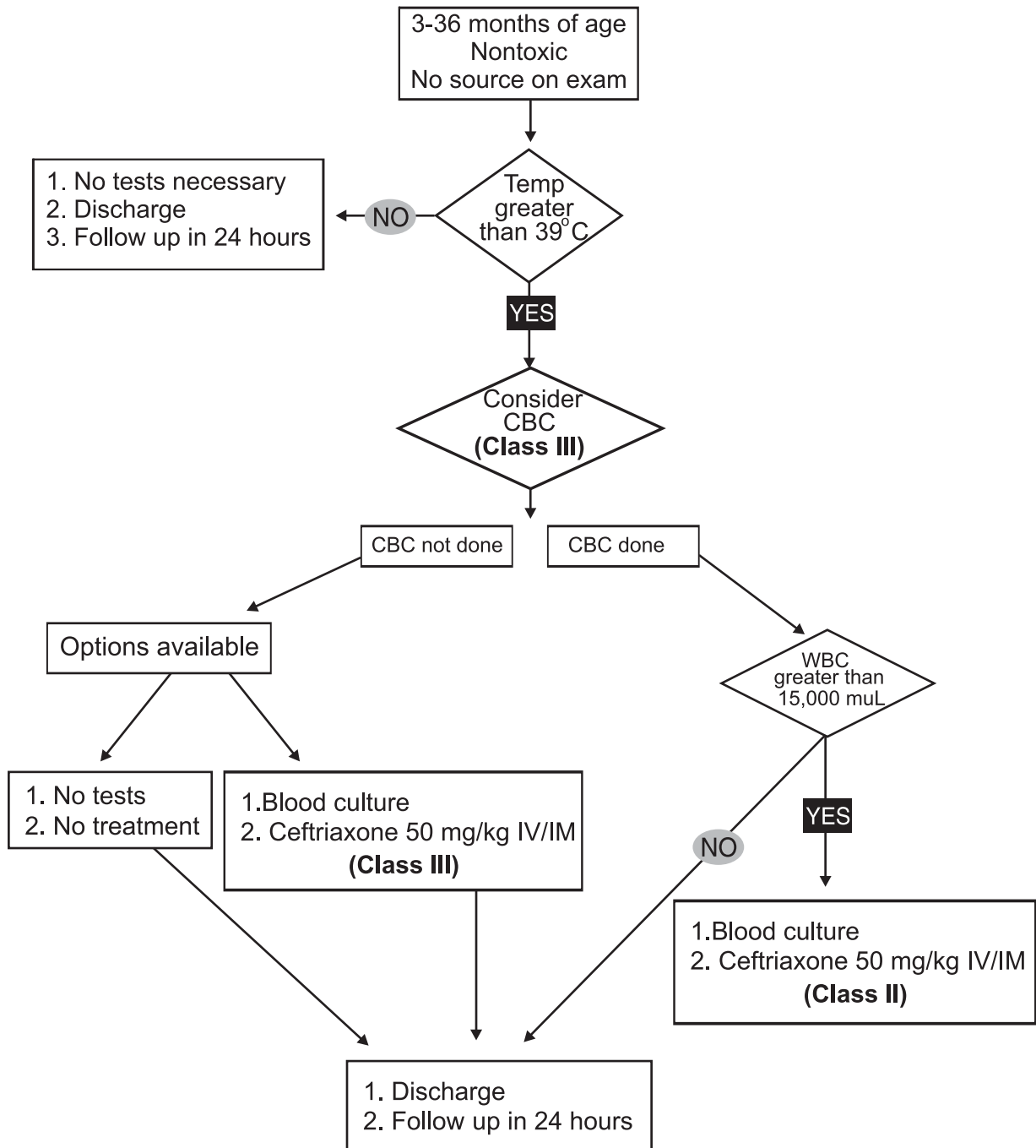
Of course, the gold standard for diagnosis of bacteremia is a blood culture that grows a recognized pathogen. In general, any patient treated expectantly for suspected bacteremia should probably have a blood culture obtained prior to initiation of antibiotics in order to maximize the chances that a culture will yield the responsible pathogen. However, the average time to detection of positive cultures is approximately 15 hours and may be as long as 48 hours, which does not assist the ED physician in the treatment decision-making process. In addition, the impact of a false-positive (contaminated) blood culture cannot be entirely discounted. False-positive cultures lead to substantial increases in resource utilization, unnecessary hospitalizations, and overuse of antibiotics.<sup>25,108-110</sup> Often, these costs are not considered in economic analyses of decision strategies in identifying and treating occult bacteremia. One recent report is emblematic of the current state of occult bacteremia in several aspects. Stoll and Rubin retrospectively evaluated 329 children between 2 and 36 months of age at their institution with a fever of or equal to 39°C or more in whom a blood culture had been performed prior to discharging the patients to home. There were three positive cultures (0.91%) for pathogens; all grew *S. pneumoniae*. However, two of the positive cultures occurred a month apart in a 20-month-old unimmunized child. WBC, ANC, and band ratio all failed to predict occult bacteremia. In addition, there were four (i.e., more) positive blood cultures for contaminant organisms. On this basis, Stoll and Rubin recommended abandoning the

CBC/blood culture approach in any and all children who had received at least one dose of PCV7 vaccine.<sup>51</sup>

What sort of diagnostic specimen is acceptable to make the diagnosis of a urinary tract infection? As is the case with bacteremia, the prevailing standard for UTI is the growth of a pathogenic bacterium from a urine culture. In order to distinguish UTI from bacteriuria (bacterial colonization of the urinary tract), however, a threshold level of colony-forming units (CFU) per mL of urine is invoked. For years, the standard for a positive urine culture in the adult literature has been 100,000 CFU/mL or more of a single organism. Young children cannot, as a rule, provide a clean voided specimen, however, and usually have a urine sample obtained using sterile technique by either catheterization or suprapubic aspiration. Contamination by fecal bacteria present on the perineum and in the distal urethra proscribes the use of a specimen collected by bag technique. While growth of any number of bacteria from a urine specimen obtained by suprapubic aspiration is considered significant, American Academy of Pediatrics guidelines have considered 10,000 CFU/mL or more of a single bacterium the threshold level for defining UTI in catheterized specimens.<sup>64</sup>

Urine cultures have the same limitation for the emergency physician as do blood cultures; however, information that could guide treatment decisions is not immediately available. Rapid diagnostic tests may be used to predict UTI, and several techniques have been compared for diagnostic performance. There are varying forms of urinalysis that have been utilized in the past, and these have been compared in a meta-analysis.<sup>111-112</sup> The most sensitive of these tests (i.e., the one that will miss the fewest UTIs and is, therefore, the preferred test of emergency physicians) is "enhanced urinalysis," which employs a combination of a positive result on a hemacytometer cell count (greater than or equal to 10 WBC/hpf) or the presence of bacteria on an uncentrifuged urine Gram's stain. This approach is not available in many settings, however. Urinary dipstick tests, which can assess for the presence of leukocyte esterase and/or nitrites, perform comparatively well for screening but may miss approximately 12% of UTIs and should always be backed up with a suitably obtained urine culture. A prevailing theory as to why this may be the case is that, compared with adults, urine in children may not reside in the bladder long enough for the requisite chemical reactions to occur whereby

# Clinical Pathway: Occult Bacteremia

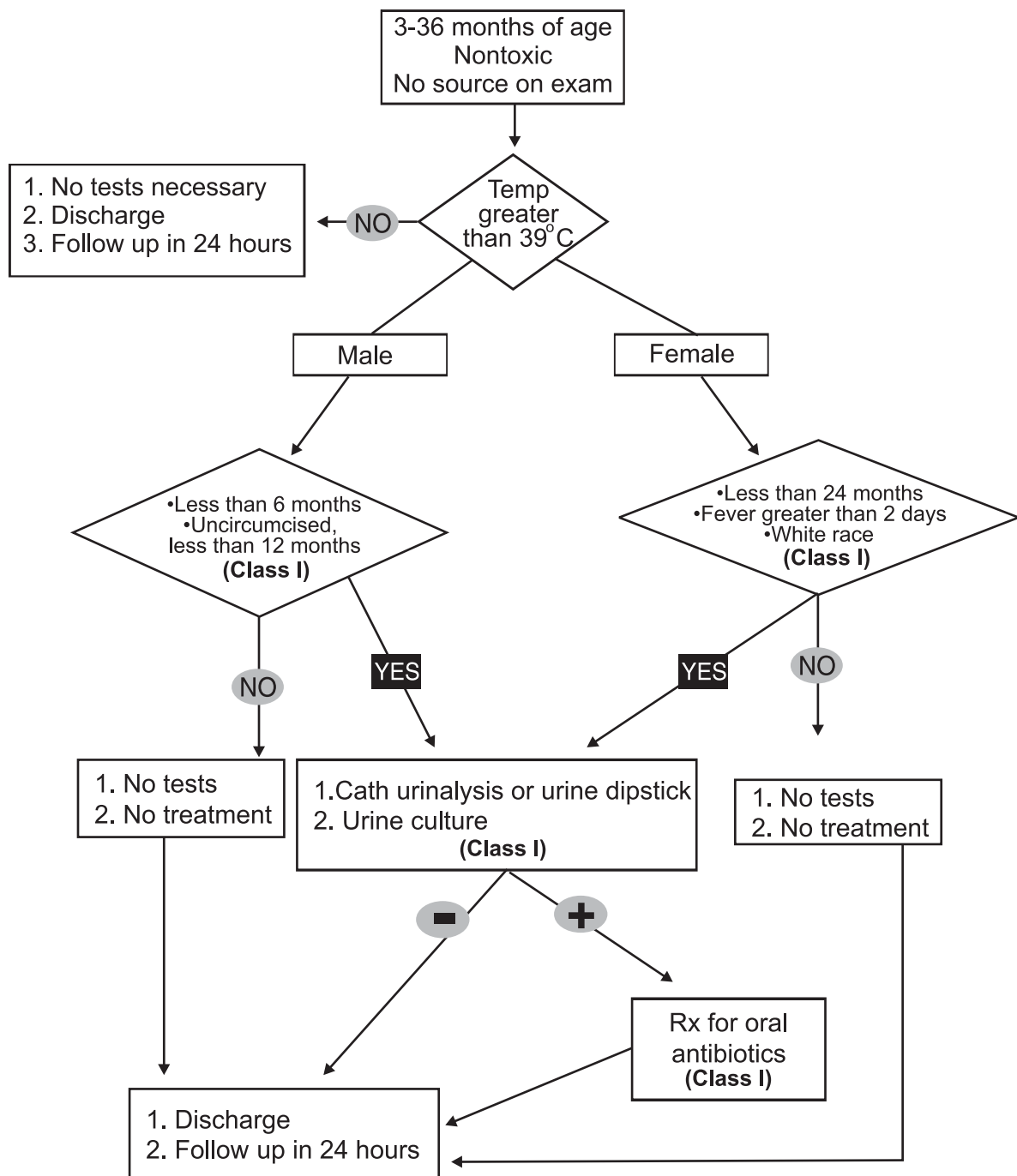


The **evidence for recommendations** is graded using the following scale. For complete definitions, see back page. **Class I:** Definitely recommended. Definitive, excellent evidence provides support. **Class II:** Acceptable and useful. Good evidence provides support. **Class III:** May be acceptable, possibly useful. Fair to good evidence provides support. **Indeterminate:** Continuing area of research.

*This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.*

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# Clinical Pathway: Occult UTI

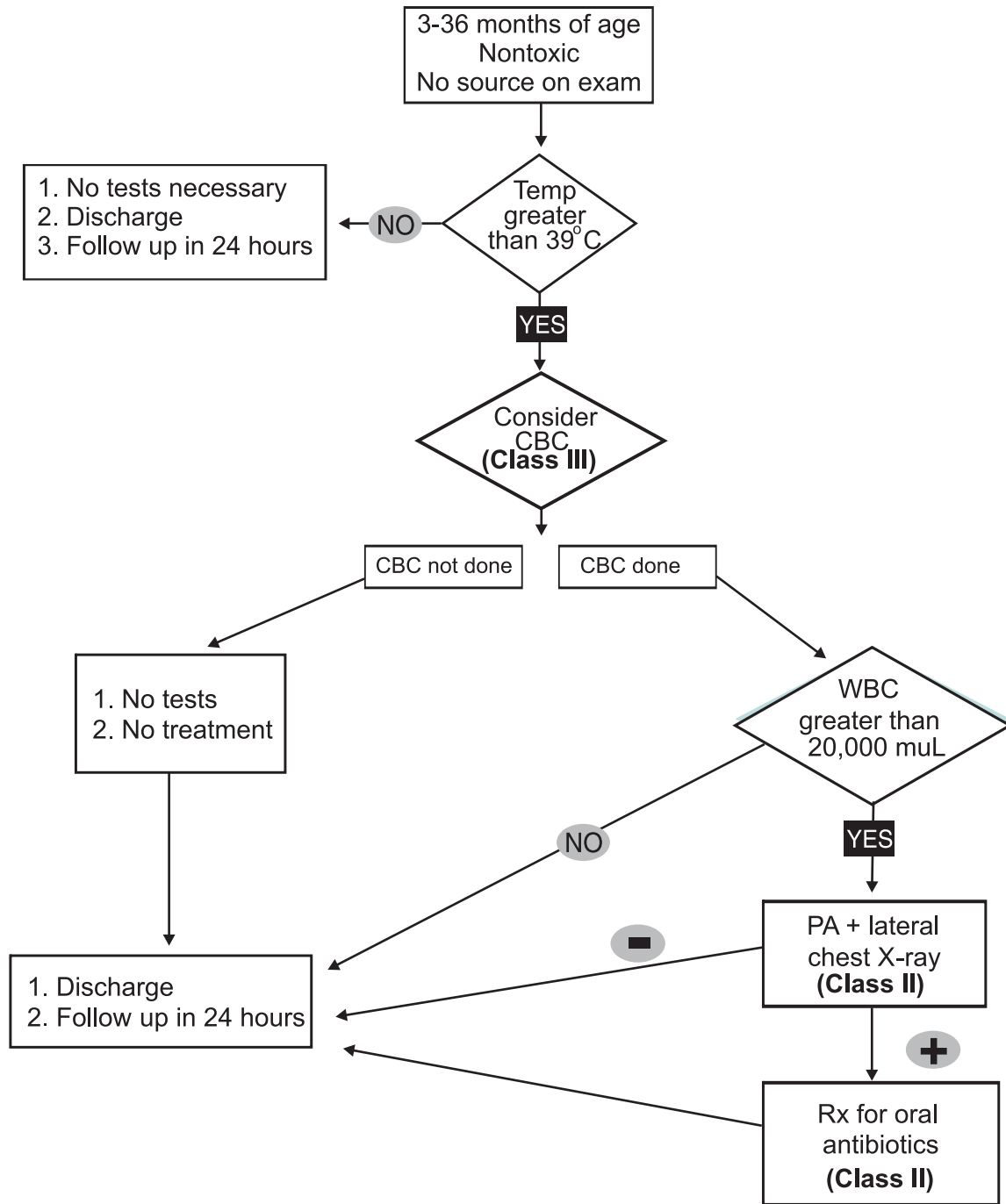


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# Clinical Pathway: Occult Pneumonia



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bacteria form nitrites and white cells accumulate elaborating leukocyte esterase for detection. Hence, as blood culture is essential for the diagnosis of bacteremia, urine culture remains the sine qua non for diagnosis of UTI; a urine culture should be sent on all febrile patients at risk for UTI.<sup>64,67</sup>

A study by Bachur et al. noted that children less than 5 years of age with fever of 39°C or more and no clinical examination findings consistent with pneumonia, who also had a WBC in excess of 20,000 muL had "occult" pneumonia discovered on a chest radiograph in 19%-26% of cases.<sup>113</sup> Hence, the American College of Emergency Physicians has included the consideration of a chest radiograph in patients older than 3 months with fever of 39°C or more and a WBC of 20,000 muL or more as a part of its clinical policy on young children with fever.<sup>49</sup> This presumes, of course, that a WBC is obtained in this cohort of febrile children without an apparent source, and current literature is moving rapidly away from that recommendation. As it makes little sense to obtain one screening test in order to beget another screening test, it remains to be seen what the impact of these data will be. But, in the case where a WBC has already been obtained on a patient with fever without source and it exceeds 20,000 muL, a chest radiograph should be strongly considered.

## Treatment

### Occult Bacteremia

Prior to the late 1980s, long-acting broad-spectrum outpatient antibiotic therapy was unavailable, and empiric treatment of suspected bacteremia in pediatric outpatients was undertaken with simple oral agents, such as amoxicillin. At that time, microbial resistance through  $\beta$ -lactamase inhibition was much less common, and the majority of the organisms responsible for bacteremia (*S. pneumoniae*, HIB, and *N. meningitidis*) were susceptible to penicillins. Several studies during this era documented a trend toward better outcomes (fewer subsequent soft-tissue infections, fewer instances of persistent bacteremia, and fewer hospital admissions) in bacteremic patients treated with oral antibiotics compared with those who went untreated.<sup>11,27</sup> However, there were insufficient data to conclude that oral antibiotics prevented meningitis, the SBI of greatest concern.

Ceftriaxone's arrival gave physicians a powerful weapon in their arsenal. Parenteral administration

of ceftriaxone conferred broad-spectrum coverage against the most prevalent bacteria responsible for SBIs and lasted 12-24 hours. Several investigations suggested that ceftriaxone was superior to amoxicillin and effective in preventing the most feared sequela of bacteremia: meningitis.<sup>12,29</sup> However, as alluded to earlier, the methodology of at least some of these studies came into question because the denominator used to calculate results was the number of cases of proven bacteremia rather than cases of fever (i.e., those at risk for bacteremia). Again, the treatment of documented bacteremia has never been controversial. Concern over ceftriaxone's ability to mask progression of invasive disease was raised, but despite the cautionary tone of a vocal minority,<sup>34-35</sup> the use of ceftriaxone rapidly took on standard-of-care status, in essence replacing clinical judgment as a treatment standard. This phenomenon was highlighted in a 2002 paper by Jain and Sullivan, who examined ceftriaxone use in their institution and compared it with established practice guidelines. Ceftriaxone had been used 289 times in 229 patients during the period they examined. In only 40 of these 229 patients (17.5%) was it administered in accordance with guidelines; 43 of 229 (18.8%) uses were questionable; and a full 146 of 229 (63.7%) uses were unjustified. Incidentally, the rate of positive blood cultures in their sample was 3 out of 229 (1.3%).<sup>41</sup>

In practical terms, because viral disease is much more prevalent than bacterial disease among febrile 3-to-36-month-olds, because there is still no consistently reliable method for prospectively pinpointing which of these patients is bacteremic, and because only a small proportion of bacteremic patients go on to develop serious sequelae, a relatively large number of febrile children need to be treated with antibiotics of some kind in order to prevent a single episode of either SBI or, in particular, meningitis. A meta-analysis by Bulloch et al. from 1997 estimated the number of febrile patients needed to treat to prevent one episode of SBI is 414 patients. The estimated number of patients needed to treat with ceftriaxone as opposed to oral antibiotics in order to prevent one case of meningitis was 3789 patients. Presumably, both of these numbers are even greater today. The conclusions of the meta-analysis were that although there was a trend toward reduced risk of SBI with the empiric use of either oral or parenteral antibiotics, the effect was insignificant and many children would be treated unnecessarily to achieve this effect.<sup>31</sup> In addition, regarding *S. pneumoniae* disease

(responsible for the bulk of bacteremic illnesses), there was no difference in the rate of subsequent SBI between patients treated with oral or parenteral antibiotics. So, in today's environment, is empiric treatment for occult bacteremia justified? The jury is still out.

In this day and age of evidence-based medicine (EBM), even the EBM gurus pay homage to the value of clinical judgment in these difficult decisions. Literature evidence is incomplete without bringing the clinician's experience and judgment to bear. It's the clinician's role to put broad population data in the context of the individual patient sitting in front of him or her at this moment in making clinical decisions. Also, taking the family's stance into consideration in this regard may not be unreasonable under the circumstances. As Green and Rothrock asked, are you a "risk-minimizer" or a "test-minimizer"?<sup>114</sup>

### Occult Urinary Tract Infection

Any young patient who has a positive urinary screening test result, whether from dipstick or a form of urinalysis, should be presumed to have a UTI and started on antibiotic therapy. Even in the presence of fever, and therefore presumed pyelonephritis, treatment may be safely conducted on an outpatient basis with oral antibiotics given that the patient appears nontoxic and is able to tolerate oral fluids.<sup>115</sup> The initiation of treatment with a parenteral dose of ceftriaxone does not add any benefit in patients with UTI.<sup>116</sup> Oral antibiotics should be adjusted to fit prevailing local bacteriology and sensitivities, as there is considerable variation by community. Reasonable outpatient options include cefixime (8 mg/kg dose twice on the first day, then 8 mg/kg/day divided QD or BID thereafter) or trimethoprim-sulfamethoxazole (8-10 mg/kg/day of the trimethoprim component divided BID). Treatment should be prescribed for 7-14 days.

### Occult Pneumonia

Most previously healthy pneumonia patients over the age of 3 months are treated on an outpatient basis. Associated factors that would warrant admission for inpatient therapy include 1) presence of an underlying condition (e.g., congenital heart disease) that may be exacerbated by pneumonia; 2) presence of hypoxia; or 3) inability to tolerate oral medications (e.g., vomiting/dehydration). Typical therapy is similar to that for other respiratory infections, such as otitis media: a penicillin, such as amoxicillin (80

mg/kg/day divided BID or TID), or a macrolide, such as azithromycin (10 mg/kg/day once on the first day and 5 mg/kg daily for four days thereafter). Other than azithromycin, most antibiotics are prescribed for 7-10 days, though there is no solid evidence to support this duration of therapy.

### Special Circumstances

Current immunization recommendations are for children to receive doses of HIB and pneumococcal vaccine (PCV7) at 2, 4, and 6 months of age and a booster at 12-18 months. The first three doses are thought to confer primary immunity. Although there is a relatively low incidence of invasive bacterial disease in the 3-to-6-month age range, recommendations vary on whether to aggressively seek occult bacteremia in this age group because of their incomplete vaccination status. One current study suggests that receiving one immunization with PCV7 was sufficient to obviate further investigation.<sup>51</sup>

Populations who may not have received protective immunizations, such as immigrants or those whose parents are "conscientious objectors" to immunizations, likely warrant a more conservative approach similar to that for special populations who are immunocompromised. Screening and empiric antibiotic therapy may still play a significant role in these groups, and today, many clinicians' decisions whether to pursue occult infection and treat with empiric antibiotics turn primarily on the patient's immunization status and the ready availability of follow-up.

### Controversies/Cutting Edge

#### SBI In The Presence Of Viral Illnesses

Greenes and Harper reported in 1999 that children 3 to 36 months of age with a recognizable viral syndrome (RVS) had a negligible rate (0.2%) of bacteremia when compared with febrile patients without RVS and, therefore, need not have a blood culture performed. For the purposes of their investigation, RVS was defined as clinical croup, varicella, bronchiolitis, or stomatitis.<sup>117</sup> Since that time, investigations seeking to limit the unnecessary pursuit of occult infection have taken advantage of rapid diagnostic tests for viral illnesses, such as respiratory syncytial virus (RSV) or influenza. At least two studies of children less than 3 months of age with fever and a positive rapid antigen test for RSV have been conducted to assess for the concomitant rate of SBI.<sup>118-119</sup>

While rates of bacteremia in children with documented RSV were found to be lower than those without RSV, there remains a clinically relevant rate of UTI in the RSV-positive group (5%-7%). Therefore, urinary testing is still encouraged in the setting of RSV infection in this age group.

Likewise, data have appeared in the literature comparing febrile children 3 to 36 months of age with a positive rapid influenza antigen test with those with negative flu tests. The rates of all SBI were lower in the flu-positive groups (9.8% vs. 28.2%).<sup>120</sup> The relatively higher rates of SBI in this study compared with others was attributed to the manner of diagnosis of pneumonia on a chest radiograph, as patients who had radiographic interpretations of "cannot exclude pneumonia" were counted as positives. However, flu-positive patients had lower rates of bacteremia (0.6% vs. 4.2%) and UTI (1.8% vs. 9.9%) than did flu-negative patients. The use of rapid influenza antigen testing has been

shown to conserve resources, limit laboratory testing, and reduce ED throughput times in two subsequent impact studies.<sup>121-122</sup> Clearly, our more sophisticated ability to detect viral illness in this patient population is changing our approach to fever in children.

### **Advancing Diagnostic Technology**

Newer avenues are under investigation in the ongoing quest to find a rapidly available, more accurate screening test for bacterial disease in febrile children. High levels of serum interleukin-6 (IL-6) were found to be a marker in children with clinical signs of sepsis. IL-6 had a sensitivity of 91% and a specificity of 98% for invasive bacterial disease, and none of the 50 febrile patients in this study without occult bacteremia had elevated levels of IL-6.<sup>53</sup> Strait et al. subsequently compared levels of several cytokines—tumor necrosis factor- $\alpha$  (TNF), interleukin 1 $\beta$  (IL-1), and interleukin 6 (IL-6)—in 33 cases and 66 controls from a sample of 1329 febrile patients ages 0-36

## **Cost-Effective Strategies**

- 1. Order diagnostic tests when they will affect your management decision. Don't when they won't.**

If you've already decided to treat a patient (for otitis media, say) with antibiotics, forgo the CBC. If you've already decided NOT to treat a patient, getting a lab test is likewise silly. Will you attribute the result to laboratory error when it comes back abnormal? It's hard enough getting blood from those tiny veins—make sure you're going to use the answer to the question you pose.

- 2. If you do obtain a diagnostic test, act appropriately on the result.**

Ignoring an abnormal result you didn't expect or didn't check on after ordering a test is medicolegal folly. You're just leaving the weapon at the scene of the crime with your fingerprints all over it, should the patient have a bad outcome. If you do it, follow it up. If it wasn't that important, then why did you do it in the first place?

- 3. Before administering ceftriaxone to a patient, ensure that a blood culture and perhaps a urine culture have been obtained.**

Your best opportunity to isolate a pathogen is before you sterilize the patient with ceftriaxone. If the patient is toxic-sick, treatment comes

before organism identification, but in the well-appearing kid you're just checking for occult disease, maximize the chance of getting an etiologic clue.

- 4. Arranging follow-up with a primary care source is a critical step in managing pediatric fever.**

Follow up, follow up, follow up. It should be your mantra. Bounce them back to the primary care physician for a reevaluation in 24 hours. Pediatric illness can change quicker than a New York traffic light. And always make sure you tell the family to come back if anything changes and the patient goes south.

- 5. Keep an open mind—the only constant is change.**

Five to 10 years from now this article may have new and different recommendations, based on changing epidemiology of pediatric fever, diagnostic advances, and emerging resistance patterns. Stay alert! Like they told you in medical school, only half of what you learned there will be applicable by the time you retire from practice. As emergency physicians, we're used to the "adapt and overcome" approach. It's one of the things that makes us special.

## Ten Pitfalls To Avoid

1. **"The girl's urine dipstick was nitrite- and leukocyte esterase-negative so I sent her home without antibiotics and canceled her urine culture."**

While a urine dipstick exam is a quick, cheap, and helpful screening test for UTI, it is only 88% sensitive. Hence, a UTI may be missed with a negative dipstick. If you're checking the urinary tract for a source of infection, *always* send the urine culture.

2. **"I know his white blood cell count was only 12,000/L, but with a fever of 103°F, I felt it best to give him a shot of ceftriaxone before discharging him."**

The peripheral WBC is a poor screening test for occult bacteremia. A WBC less than 15,000/L has a high positive predictive value (PPV) for viral infection. (For that matter, so does a WBC greater than 15,000/L!) If you're going to invoke the guidelines, at least follow them. Otherwise, you're likely merely contributing to resistance!

3. **"She's got minimal upper respiratory symptoms, but her RSV is positive, so I've got my source of infection."**

A positive RSV test *may* explain the patient's fever completely. But don't forget to consider the urine as a concomitant source—3%-7% of RSV-positive children are also harboring UTIs.

4. **"The child's white blood cell count came back from the lab at 18,500/L, but he looked great and Mom was anxious to go home, so I discharged him without antibiotics. I hope he's OK."**

See #2 above. If you're not going to act on the WBC result, don't send it! While the guidelines are just guidelines, they will be invoked by the plaintiff when there's a bad outcome and you fail to explain why you didn't treat someone clearly at risk for SBI. It's easier to justify not getting the test than it is failing to act on an abnormal result.

5. **"Billy has a raging left otitis media, but I don't think that fully explains his fever of 104.2°F. I'm sending a CBC on him."**

Are you going to treat him with antibiotics anyway? What will the CBC add? What's the typical WBC in a patient with acute otitis media anyway? (Do you usually send one???) Fearing disease we can see more than disease we cannot is absurd. Don't waste your or the patient's time on this test. Sure as shootin' this is the one CBC that the lab will call to say has clotted—45 minutes later.

6. **"José and his family just moved to the States and don't have a PCP yet. Despite his fever, he looked pretty good, so I told them they need to find themselves a doctor and sent them on their way."**

Recall that the unvaccinated—and this likely includes José—are at higher risk of bacteremia from organisms for which we now routinely immunize in the US. This guy needs a lab workup and perhaps prophylactic antibiotics before discharge. Also, it is incumbent on us to arrange more specific follow-up for high-risk situations like this one.

7. **"I know Keisha has sickle-cell disease, but her temperature is only 101°F and everybody in her family has got a cold right now. I think we're safe calling this thing a virus and having her follow up on Monday."**

Write that check to your malpractice attorney right now. Sickle-cell disease renders its victims immunocompromised, particularly against encapsulated organisms such as *S. pneumoniae* and HIB. Keisha should also undergo a workup; if everything looks good and she has follow-up in the next 24 hours, she can be managed as an outpatient with ceftriaxone on board.

8. **"Two-year-old Joey was transferred here for fever, a WBC of 22,000/L, and belly pain, but his urine is clean and his abdominal CT was negative. He looks good now after IV fluids and some acetaminophen. I think he's just got a virus."**

Joey is a prime candidate for occult pneumonia. Despite the fact that his lungs sound great, get a chest film in this instance. It's a lot less radiation than that CT scan.

9. **"Mom says 18-month-old Sandra's fever at home was 103°F and she looked just terrible, but here in the ED she's playful and afebrile. No way she has a bacterial infection."**

Response to antipyretics has not been shown to reliably predict either the presence or absence of SBI. That Sandra looks great now puts her in the febrile nontoxic category. Think about at least grabbing a urine sample here.

10. **"I'm waiting on the CBC. If his WBC is up, I'm going to tap this kid."**

At least in the under-3-month crowd, peripheral WBC is poorly predictive of the presence of meningitis, and a normal WBC can be falsely reassuring. As the child gets beyond 3 to 6 months, the clinical exam becomes more reliable in assessing for signs of meningitis, and your clinical judgment regarding whom to tap becomes more reliable. But the principle is a good one: base the decision to perform a lumbar puncture on your clinical assessment of the likelihood that your patient has meningitis and independent of any laboratory parameter.



months enrolled in the study. While an IL-6 level greater than 95 pg/mL was found to be a better predictor of bacteremia (sensitivity 88%, specificity 70%, PPV 7%) than WBC and at least as good as ANC, its greatest utility was in combination with an ANC greater than 5000 muL (sensitivity 100%, specificity 78%, PPV 10.4%). TNF and IL-1 had no clinical utility in this endeavor. However, the wide overlap of values for IL-6 between cases and controls detracted from its usefulness, and the assay took several hours to complete, making it impractical for emergency department use.<sup>55</sup>

Serum procalcitonin (PCT) levels have been used clinically in Europe for some time and seem to have potential for distinguishing between viral and bacterial disease. Much of the data derives from studies of infants or special populations (e.g., febrile neutropenic cancer patients). One prospective multicenter trial of 445 febrile patients between 1 and 36 months of age, however, found PCT to be more specific than CRP, with similar sensitivity in separating bacterial from viral disease, but also better than CRP in detecting invasive infection as compared with noninvasive infection.<sup>59</sup> Neither indicator is ideal by itself, however, and experience with PCT in the United States has been limited.<sup>61</sup>

Other assays specific for pneumococcal disease have been proffered as alternative testing methods. Isaacman et al. evaluated a serum polymerase chain reaction (PCR) assay for pneumococcal DNA in 480 febrile study patients and 106 afebrile controls. Twelve (57%) of the 21 patients with documented *S. pneumoniae* bacteremia had positive PCR tests. However, 206 patients from the study group and 16 of the controls who had negative blood cultures also had positive PCR results. While PCR technology has promise, the level of sensitivity and specificity the assay offers precludes its use as a screening test at this time.<sup>57</sup>

Neuman and Harper performed an interesting study to assess the usefulness of a rapid urine antigen assay for pneumococcal disease. Over a 15-month period, they collected samples from patients aged 3 months to 5 years in five distinct categories: 1) those with documented *S. pneumoniae* bacteremia; 2) febrile children with a diagnosis of pneumonia; 3) febrile nonbacteremic patients with an elevated WBC; 4) febrile nonbacteremic patients with a normal WBC; and 5) afebrile children with no evidence of a current or recent infection. Of the 346 enrolled patients, the urine assay was positive in 23/24 (95%)

patients with pneumococcal bacteremia; 47/62 (76%) of those with a lobar pneumonia on a chest radiograph; 28/181 (15%) nonbacteremic patients with fever, with no difference whether their WBC was normal or elevated; and in 6/79 (8%) of those without fever or other signs of infection. They concluded that the urine pneumococcal antigen assay was highly sensitive for proven and suspected bacteremia as well as invasive pneumococcal infection. Its false-positive rate of approximately 15% left something to be desired, but its performance parameters compared favorably with the use of WBC or ANC.<sup>58</sup>

### Changing Epidemiology: Resistant Microbes

The past several years have seen a perceptible worldwide increase in the number of infections with resistant bacteria, likely a consequence of rampant and perhaps indiscriminate antibiotic use. We have witnessed the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and other pesky organisms. While pneumococcal vaccine has already dramatically decreased the rate of SBI in young children, including a decline in the overall rate of invasive pneumococcal disease, some authors still preach caution and are not ready to abandon their screening and treatment strategies just yet. They point out that PCV7 immunizes against only the more common serotypes of pneumococcus, that immunization rates are not fully 100%, and that some children may lack the ability to mount an adequate immune response to vaccination. And, while they grant that the overall rate of invasive pneumococcal disease is lower, there is an ominous increase in the percentage of invasive disease cases caused by nonvaccine strains.<sup>123</sup> According to these investigators, we may merely be selecting for more virulent strains through our vaccination efforts. This is all the more reason to be discriminating in our application of diagnostic tests as well as our use of antimicrobials.

### Disposition

Toxic-appearing patients and those with underlying medical conditions placing them at risk of invasive bacterial infection should receive a comprehensive evaluation, including cultures of relevant sites and empiric broad-spectrum antibiotic therapy. They should be hospitalized and treated expectantly pending culture results.

Patients who have a coincident medical problem

beyond fever (wheezing, dehydration, etc.) should be treated appropriately and be considered for hospital admission based upon parameters relevant to these conditions (e.g., ability to tolerate oral fluids). If sent home after a period of observation, follow-up with their primary care source in the next 24 hours is recommended. Phone communication with the primary care physician prior to discharge is also recommended.

Whether the ED physician chooses to perform a laboratory workup and/or treat with antibiotics, the nontoxic-appearing febrile child with no apparent source of infection on exam may be safely discharged from the emergency department. Follow-up with a primary care provider in 24 hours is crucial. If follow-up with the patient's physician is not possible, the caregivers should be encouraged to bring the child back to the emergency department for a recheck. Families should also be provided with clear instructions on when to return to the emergency department sooner than their arranged follow-up appointment. Conditions that would warrant a revisit to the emergency department include any alteration in mental status (lethargy, irritability, seizure activity), evidence of dehydration (absence of tears, saliva, or urine), or new physical findings that may point to an infectious source (rash, productive cough). The caregivers should be counseled regarding symptomatic measures, such as administration of antipyretics and encouragement of adequate amounts of oral fluids.

In many instances such as this, reassurance, clear instructions regarding what to look for, and encouragement of follow-up evaluation with a primary care source may be the most important things the emergency physician can provide.

## Summary

The approaches to managing fever in children continue to shift with time. Perhaps that's what makes it difficult to obtain a comfortable foothold or consistent approach with this clinical entity. On the upside, serious bacterial illness in the 3-to-36-month age group is becoming less prevalent due to advances in immunization medicine. We have ever more powerful antibiotics at our disposal. And our diagnostic techniques are consistently becoming more precise. On the other hand, our past overzealous use of antibiotics, driven in part by a lay community and a medicolegal climate that demand cer-

tainty in diagnosis and cutting-edge remedies, has opened a Pandora's box of antimicrobial resistance. The serious bacterial illnesses we see now are more virulent and resistant to our usual tactics. At the front end of the continuum of medical care, emergency physicians are often the greatest stewards of medical resources and need more than ever to exercise restraint in the management of illness and injury, with an eye toward our collective future. These days, giving patients a shot of ceftriaxone and sending them out the door may be doing more harm than good, and we must be more discreet and judicious in our therapeutics.

Our surgical colleagues will tell us that the reason a surgeon's training is so extended is not so much to learn surgical *technique* as it is to acquire surgical *judgment*—the knowledge of when to operate and, as important, when not to. Likewise, despite all the technological advances that have come down the pike, the practice of emergency medicine requires exercising clinical judgment now more than ever. Having sophisticated tools at our disposal does not constitute an indication for their use. As we are all aware, no laboratory test affords complete reassurance of a disease or condition's presence or absence. The use of any diagnostic technique should

## Key Points

- While serious bacterial illness (SBI) may be present in a nontoxic-appearing, febrile (T greater than 39°C) child between 3 and 36 months of age, the vast majority of these patients have self-limited viral infections.
- Immunizations against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* have dramatically reduced the rate of occult bacteremia and invasive infection due to these organisms.
- There is still no rapid, inexpensive, and sufficiently sensitive and specific diagnostic test available to distinguish patients with SBI from those without SBI.
- A significant proportion of febrile children less than 36 months of age (~5%) have occult urinary infection and already have evidence of renal injury at the time of diagnosis.
- No screening test for urinary infection is sufficiently sensitive to detect all UTIs; always send a urine culture in patients you investigate for UTI.
- There are no definitive data to suggest that empiric antibiotic treatment (either oral or parenteral) prevents serious sequelae from bacteremia to a significant degree.
- Increasing antimicrobial resistance mandates the exercise of restraint in the administration of antibiotics, particularly broad-spectrum antibiotics such as ceftriaxone in the pursuit of occult infection.

be used to modify one's estimate of the probability of disease, based on clinical assessment, and to move the probability upward above the threshold at which one will decide to treat, or downward below the threshold at which one will decide not to treat.

Otherwise, a test has limited usefulness. As the probability of certain conditions (e.g., bacteremia or UTI) varies, the utility of the tests employed to diagnose them must also change. It is critical that we remain aware of these changing probabilities, as that knowledge is at the crux of our medical expertise.

With the febrile child, as in all things, it is important that we understand our questions, know what our tools and our remedies can accomplish for us and what they cannot, and understand our own level of risk tolerance before diving into a formulaic workup. The published guidelines are simply guidelines, after all, and were never intended to be a precise recipe. Even the guidelines contain that caveat.<sup>45</sup> Consider each patient and each situation individually. Particularly in these times of emphasis on astute resource management, we owe it to ourselves. Moreover, we owe it to our patients.

## References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, are included in bold type following the reference, where available.

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## CME Questions

The CME print semester starts with the January issue and restarts with the June issue. The CME questions are numbered consecutively. Current subscribers can take the test in print every six months or online monthly.

- The widespread implementation of vaccine(s) directed against which organism(s) led to a fall in bacteremia rates?**
  - Streptococcus pneumoniae
  - Haemophilus influenzae type B
  - Bordetella pertussis
  - a and b above
  - All of the above
- Which organism is the most prevalent cause of occult bacteremia in the 3-to-36-month age group?**
  - Staphylococcus aureus
  - Haemophilus influenzae type B
  - Escherichia coli
  - Streptococcus pneumoniae
  - Neisseria meningitidis
- Of the following, the least sensitive serum screening test for serious bacterial infection is:**
  - The absolute neutrophil count
  - The band-neutrophil ratio
  - The total white blood cell count
  - C-reactive protein level
  - Procalcitonin level
- Risk factors for urinary tract infection in girls less than 24 months include all of the following, EXCEPT:**
  - Presence of fever for more than 2 days
  - African American race
  - Fever greater than 39°C
  - Absence of another apparent fever source
  - Age less than 12 months
- Traditionally, what percentage of pneumococcal bacteremia resolves spontaneously, without treatment with antibiotics?**
  - Less than 5%
  - 25%
  - 50%
  - 75%
  - Greater than 90%

**6. PCV7 (Prevnar) confers immunity against:**

- a. The seven pneumococcal serotypes responsible for most infections
- b. Invasive pneumococcal disease, such as meningitis or osteomyelitis
- c. Infections due to all pneumococcal serotypes
- d. Serious bacterial infections (SBIs)
- e. Pneumococcus, chlamydia, and varicella

**7. In a pediatric patient with fever, a peripheral WBC greater than 15,000 muL has the best positive predictive value (PPV) for:**

- a. *Streptococcus pneumoniae*
- b. *Haemophilus influenzae* type B
- c. *Neisseria meningitidis*
- d. Bacteremia of any source
- e. Viral infection

**8. An 18-month-old circumcised male with fever to 100.5°F rectally who appears toxic on examination should undergo what extent of laboratory workup?**

- a. No tests are necessary
- b. Catheterized urinalysis and urine culture only
- c. Blood culture only
- d. CBC and blood culture if WBC greater than 15,000 muL
- e. Comprehensive workup searching for an infectious source

**9. The performance of a urinary dipstick in a child with fever:**

- a. Obviates the need for a urine culture if it is negative
- b. Is superior to an enhanced urinalysis
- c. Is a time-consuming, costly process
- d. Is a useful screen for UTI if nitrite- or leukocyte esterase-positive
- e. Must be confirmed by microscopy before initiating treatment

**10. Ceftriaxone:**

- a. May be administered IV, IM, or PO
- b. Has been definitively shown to prevent meningitis in bacteremic patients
- c. Is superior to oral antibiotics in eradicating bacteremia
- d. Enhances the treatment of UTI with oral antibiotics
- e. Crosses the blood-brain barrier

**11. The rate of bacteremia in 3- to 36-month old children:**

- a. Has remained steady over the past 30 years
- b. Increases as the height of fever increases
- c. Is greater in boys than it is in girls
- d. Approximates 14% in the youngest (3-6 month) age group
- e. Is primarily due to *H. influenzae* infection

**12. At present, a serum PCR-based pneumococcal assay:**

- a. Is widely available, rapid, and inexpensive
- b. Is highly specific (few false positives)
- c. Is highly sensitive (few false negatives)
- d. Has potential to assist in the diagnosis of pneumococcal disease
- e. Is a validated screening test for pneumococcal disease

**13. Patients with recognizable viral syndromes (RVS):**

- a. Have a comparable rate of SBI to those patients without RVS
- b. Must have the source of their viral infection documented by a rapid antigen test
- c. May still merit investigation for a concomitant UTI
- d. Generally have lower-grade fevers than patients with bacterial infections
- e. Do not necessarily require antibiotics but should have a blood culture performed

**14. Patients with sickle-cell disease and fever:**

- a. Require a comprehensive search for a bacterial source of infection
- b. Do not need a WBC—it's usually higher in these patients anyway
- c. Are protected against UTI due to carbohydrate secretion in the urinary tract
- d. Are often infected by bacteria resistant to ceftriaxone
- e. Have normal splenic function until the age of 5 years

**15. The most common etiology for pneumonia in the 3-to-36-month old age group is:**

- a. *Streptococcus pneumoniae*
- b. *Mycoplasma pneumoniae*
- c. *Bordetella pertussis*
- d. *Chlamydia pneumoniae*
- e. Viral infection

## 16. Urinary tract infection in the 3-to-36-month old age group:

- Occurs with equal frequency in girls and boys
- May present with nonspecific symptoms
- Usually requires inpatient intravenous antibiotic therapy
- Is rarely associated with pyelonephritis
- Is less frequent in Caucasian girls than in African-American girls

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Each action in the clinical pathways section of *Pediatric Emergency Medicine Practice* receives a score based on the following definitions.

### Class I

- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

### Level Of Evidence:

- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

### Class II

- Safe, acceptable
- Probably useful

### Level Of Evidence:

- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case-control studies
- Less robust RCTs
- Results consistently positive

### Class III

- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

### Level Of Evidence:

- Generally lower or intermediate

### levels of evidence

- Case series, animal studies, consensus panels
- Occasionally positive results

### Indeterminate

- Continuing area of research
- No recommendations until further research

### Level of Evidence:

- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA* 1992;268(16):2289-2295.

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