ABSTRACT: Occult bacteremia now occurs in only 1 of 200 children who present with acute fever (temperature of 39°C [102.2°F] or higher) and white blood cell counts of 15,000/µL or more. The most likely cause of bacteremia remains *Streptococcus pneumoniae*; when there is no evidence of toxicity, such bacteremia is generally a benign, self-limited event. Because of the extremely low yield, blood cultures are no longer routinely warranted in children aged 3 to 36 months who have no obvious source of infection, and empiric treatment of occult bacteremia is no longer appropriate. Almost all cases will spontaneously resolve with a low rate of subsequent focal infection. If a child remains febrile and worsens clinically, further diagnostic evaluation and possible empiric treatment with antibiotics pending results of cultures may be considered.

Blood cultures and empiric antibiotic therapy have been the standard of care for children 3 to 36 months of age with a temperature of greater than 39°C (102.2°F) whose white blood cell (WBC) count exceeds 15,000/µL. For a variety of reasons, however, there is now a clear need to reexamine our conventional approach to the management of febrile children. In this article, we explain why empiric therapy for low-risk children or those without a toxic appearance is no longer appropriate, and we outline current treatment guidelines.

**HOW WE GOT TO THIS POINT**

Occult bacteremia-manifesting with elevated temperature and without a focus of infection—was initially termed "pneumococcal fever" during the 1970s and early 1980s when *Streptococcus pneumoniae* was recovered in approximately 5% of blood cultures from young febrile children with mild upper respiratory tract changes (Table 1). Such changes included inflammation of the tympanic membranes, pharyngeal erythema, sinus clouding, and interstitial markings on chest roentgenograms.

In studies conducted before 1990, *S pneumoniae*, *Haemophilus influenzae* Type b (HIB), and *Neisseria meningitidis* were recovered from approximately 75%, 20%, and 5%, respectively, of positive blood cultures in patients with occult bacteremia, with occasional isolates of *Salmonella* and *Staphylococcus aureus* identified. Severe infections subsequently developed in 20% of children with *H influenzae* isolates and 50% with positive meningococcal blood cultures, but in fewer than 6% of pneumococcal occult bacteremia cases. The major concern, therefore, was centered around the first 2 pathogens.

Clinical investigations conducted in the late 1980s and early 1990s on febrile high-risk children demonstrated that antimicrobial treatment-either oral or parenteral-improved the outcome for children with suspected bacteremia. A consensus paper published in the official journal of the American Academy of Pediatrics (*Pediatrics*) in July 1993 concluded that "children 3 to 36 months of age with fever greater than 39°C and whose WBC count is 15,000/µL or more should have a blood culture and be treated with antibiotics pending culture results." This practice guideline was extremely influential among pediatricians and primary care physicians in their management of infants and children with fever.

Data during the 1990s (including a study conducted in Boston from 1993 to 1996 in febrile children who were 3 to 36 months old) indicated that the only organism commonly responsible for bacteremia in the "post–HIB era" is pneumococcus, accounting for 92% of isolates, with much less frequent identification of *Salmonella* (5%) and group A β-hemolytic streptococci (1%). However, of almost 10,000 blood cultures obtained in this study, only 1.6% were positive (see Table 1). The authors emphasized that the total absence of HIB as a cause of bacteremia was a consequence of universal vaccination against this pathogen.

More recent studies have looked at the impact of the heptavalent pneumococcal conjugate vaccine (PNCV7) on pneumococcal bacteremia and invasive disease. Since this vaccine was introduced, there has been a 70% to 90% reduction in bacteremia and pneumococcal invasive disease. There is
also evidence of a herd effect, a modest reduction of disease caused by non-vaccine strains, and a
decrease in antibiotic resistance among strains causing disease.\textsuperscript{11} By 2001, the overall rate of
invasive pneumococcal disease in children younger than 2 years had declined by 78\%.\textsuperscript{12}
Another study focused on medical visits for pneumonia or invasive pneumococcal disease.\textsuperscript{13} For
Medicaid patients in Tennessee, emergency department visits for these indications had decreased by
18\% and outpatient visits by 17\%. In New York, outpatient visits had declined by 34\%. Experience to date would now confirm that among children who have received both HIB and PNCV7
vaccines, and who subsequently have an episode of high fever and leukocytosis, the rate of
bacteremia would be lower than 0.5\%.

The primary concern with bacteremia is that serious infections, such as meningitis, may develop in
some infected children. The best documentation of these more serious consequences of
pneumococcal bacteremia was published in the 1970s; in this report, 6\% of cases of pneumococcal
bacteremia resulted in severe infection.\textsuperscript{5} We can now calculate the risk of severe infection today in
patients who present with fever and no focus of infection. Using data collected between 1993 and
1996,\textsuperscript{10} most (92\%) bacteremia is pneumococcal, but it is greatly reduced in incidence (70\% to 90\%)
among children who have been immunized.\textsuperscript{11} In short, it appears that over 3000 blood cultures would have to be obtained to pick up a single case of
bacteremia that might result in severe infection. At this rate, empiric testing and treatment would
certainly not be cost-effective. This reflects current experience throughout the country\textsuperscript{14} and
emphasizes the need to reexamine our conventional wisdom as it pertains to the management of
febrile children. Empiric therapy for low-risk children or for those who do not appear toxic is no
longer appropriate.

**CLINICAL AND LABORATORY FEATURES**

At present, the only organism that must be considered as a frequent pathogen for occult bacteremia
is *S pneumoniae*. Therefore, we will focus on this single bacterium.

In the absence of apparent toxicity, pneumococcal bacteremia is a benign, transient, and self-limited
event.\textsuperscript{7,8,10,15} It should be differentiated from bacteremia involving more virulent organisms and from
sepsis, in which blood cultures are repeatedly positive and the patient exhibits signs and symptoms
of severe illness.\textsuperscript{16,17} Repeated positive cultures also suggest the development of a focal
infection.\textsuperscript{16-18}

Earlier studies of pneumococcal bacteremia in children identified a significantly higher incidence of
infection in patients aged 7 to 12 months with temperatures of 39.4°C to 40.6°C (103°F to 105°F)
and WBC counts above 20,000/µL.\textsuperscript{8} Another study reported a 3-fold greater incidence of bacteremia
when the WBC count was over 15,000/µL and the erythrocyte sedimentation rate (ESR) exceeded 30
mm/h.\textsuperscript{19} Other studies, however, varied in their support of and conclusions about whether the WBC
count is a useful indicator for bacterial disease.\textsuperscript{20} In one report, only 6.9\% of patients with a WBC
count above 15,000/µL were found to be blood culture–positive, whereas 35\% of the bacteremic
patients had counts below 15,000/µL.\textsuperscript{3,6}

Febrile seizures have been a presenting symptom is as many as 67\% of patients with pneumococcal
bacteremia.\textsuperscript{1-4,21} This association is difficult to interpret since both febrile seizures and pneumococcal
bacteremia are independently most common in infants and children between 6 and 36 months of
age. Occult bacteremia is also more frequent in febrile children with an initial diagnosis of an upper
respiratory tract infection/fever of unknown origin or pneumonia\textsuperscript{15} than in those with otitis media or
pharyngitis. Invasion of the respiratory passages by pneumococcus apparently predisposes to
bacteremia.

Among factors not found to affect significantly the incidence of occult bacteremia have been sickle
cell (SC) disease,\textsuperscript{22,23} hemoglobin SC disease, and SC trait.\textsuperscript{24} Most reports have not shown a gender-, race-, or socioeconomic-related predominance of the disease.\textsuperscript{5}

**EVALUATION OF SUSPECTED BACTEREMIA**

Determine the need for laboratory tests on the basis of the patient's history (including his or her
functional status [ie, toxic vs nontoxic appearance]) and the physical examination results. No single
laboratory test has yet shown sufficient sensitivity and specificity to adequately direct patient
management in cases of acute fever without an apparent focus. The single exception is a screening
urinalysis or urine culture, which is recommended for all febrile infants and young children who have
no focus of infection.\textsuperscript{25}

Bennish and associates\textsuperscript{26} found the combined quantitative C-reactive protein level and ESR to have a
better sensitivity and specificity for occult bacteremia than the total WBC count, polymorphonuclear
cell count, band cell count, or the patient's temperature. The sensitivity of all these tests, save for
temperature elevation, was increased when fever had been present for more than 24 hours.
TREATMENT

Empiric antibiotic therapy for children with high fever and no identifiable focus of infection has always been highly controversial. A prospective study by Jaffe and colleagues, which found no difference in the incidence of major infectious morbidity for occult pneumococcal bacteremia in patients receiving either oral amoxicillin or placebo, argues against empiric treatment—except for those children considered at high risk based on age (younger than 28 days) or toxicity. Antimicrobial therapy produced a more rapid defervescence in the bacteremic patients, but it did not alleviate symptoms in those who were not bacteremic. Subsequently, a meta-analysis of 10 evaluate oral antibiotic treatment studies noted only a modest decrease in the risk of serious bacterial infections in children with S. pneumoniae occult bacteremia. The authors concluded that there was insufficient evidence that oral antibiotics prevent severe infections, including meningitis. Of the 2 studies that employed parenteral ceftriaxone, one concluded that treatment was effective in preventing H. influenzae meningitis but had no effect on the long-term outcome in patients with pneumococcal bacteremia.

A meta-analysis by Baraff and coworkers that included all published data on early institution of either oral or parenteral antibiotics likewise concluded that intramuscular or intravenous ceftriaxone only had a modest impact on the incidence of H. influenzae disease.

Although an earlier study by Dashefsky and associates found meningococcus responsible for 26 (5%) of 536 cases of bacteremia, the serious nature of meningococccemia and its association with shock and disseminated intravascular coagulation have long been recognized and might influence our current approach to febrile children. In this retrospective study, meningitis developed in 2 of the 8 patients treated with oral antimicrobial agents, whereas 2 of the 4 patients who were not treated initially succumbed to fulminant sepsis and shock. Overall, meningitis or death occurred in 33% of patients with unsuspected meningococcemia.

The outcome of unsuspected meningococcal bacteremia may be related to the extent of organism replication. Sullivan and LaScola found meningitis or meningococccemia significantly more often in patients with 500 or more organisms per milliliter of blood than in those with fewer organisms. Two of 3 initially untreated patients who experienced spontaneous resolution of occult meningococcal bacteremia had concentrations of 325 and 100 organisms per milliliter. A similar finding was noted by Bell and colleagues: in their study, all patients with fewer than 15 colony-forming units of pneumococcus per milliliter of blood had occult bacteremia and no focus of infection.

ADVERSE CONSEQUENCES OF EMPIRIC TREATMENT

Ceftriaxone, a third-generation cephalosporin with an extended half-life, has provided the potential for managing many serious pediatric infections with a single daily intramuscular injection on an outpatient basis. The serum concentrations of the drug given intramuscularly are comparable to those obtained intravenously, and ceftriaxone is generally well tolerated—except for occasional diarrhea and rare anaphylactic reactions. As reviewed above, previous studies have suggested that early treatment with this antibiotic may reduce the incidence of subsequent invasive disease. Bass and colleagues also found that febrile children who were treated with ceftriaxone had a greater reduction in fever and improvement in their mean clinical scores regardless of whether they were bacteremic.

However, the real question today is whether these data are applicable now that invasive H. influenzae disease has disappeared. The old conventional wisdom to empirically treat suspected bacteremia based on concerns about early H. influenzae disease can no longer be supported. Moreover, the emerging resistance of common pathogens to β-lactam antibiotics requires that we be more judicious in our overall use of antimicrobial therapy. Withholding antibiotics in low-risk children or in those who do not appear toxic who have fever and no focus of infection is certainly one way to reduce the overall use of these agents and help reverse the trend of increasing resistance.

FOLLOW-UP

In weighing the value of empiric antimicrobial therapy for the outpatient management of fever, remember that although oral or parenteral therapy may improve the clinical appearance of children with bacteremia without decreasing the development of major focal infections, it does not benefit the much larger number of children who are not bacteremic. If you decide to institute empiric therapy with a parenteral broad-spectrum antibiotic (such as ceftriaxone or ampicillin) or an oral agent (such as amoxicillin or amoxicillin-clavulanate), schedule a follow-up visit at 24 hours. Repeat the blood culture if results of the initial blood culture are positive. After an interval history and physical examination, decide whether to continue parenteral or oral therapy. Other aspects of management depend partly on the organism responsible for the bacteremia. On the basis of virtually all studies that have observed spontaneous resolution in most cases of}
occult pneumococcal bacteremia and an infrequent rate of subsequent focal infection, it appears prudent only to plan a follow-up visit and repeat blood culture for patients who become afebrile and clinically improved following the initial visit. Admit patients who remain febrile or whose condition worsens for high-dose intravenous therapy with penicillin or with an alternative agent if there is a high local prevalence of penicillin-resistant pneumococci. In such cases, a lumbar puncture is indicated, because meningitis has been reported not only in untreated patients but also in orally as well as intravenously treated patients subsequently shown to have had occult pneumococcal bacteremia.¹

The experience with meningococcal bacteremia is not as great as with pneumococcal disease because of its less frequent occurrence. Two reports of 3 patients each have noted the resolution of meningococcal bacteremia with outpatient oral antibiotic therapy.¹ One of those reports describes 3 additional patients whose illnesses resolved spontaneously without any initial treatment.³⁰ After repeating the blood culture and performing a lumbar puncture in patients with meningococcal bacteremia, it would be prudent to hospitalize them for at least 48 hours of high-dose intravenous penicillin or cephalosporin therapy pending the follow-up blood culture result. Many would argue for a 5- to 7-day course of therapy.

**PREVENTION**

The safety and efficacy of a heptavalent pneumococcal vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) conjugated to CRM197, administered at 2, 4, 6, and 12 to 15 months of age, have been confirmed in clinical trials that included 37,000 infants and children-half of whom received the vaccine.¹¹,³² A high level of efficacy-90% for vaccine strains-in preventing invasive disease after primary immunization followed by a booster dose was achieved. Invasive pneumococcal disease, as well as the overall incidence of otitis media and pneumonia, has now been reduced considerably.

**References:**

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