

Is Ceftriaxone Useful in Management of Fever Without Focus?

Background

I was recently asked whether and when ceftriaxone should be used in management of fever in young children for whom examination shows no source of infection. This question requires understanding of occult (or unsuspected) bacteremia in children. Occult bacteremia occurs in approximately 2% to 3% of febrile children aged six months to three years of age who have temperature $>102^{\circ}\text{F}$ ($>39^{\circ}\text{C}$).¹ To screen for occult bacteremia, we use two laboratory tests: complete blood cell count (CBC) and blood culture. If the white blood cell count is $>15.0 \times 10^9/\text{L}$ or if absolute neutrophil count is $>10.0 \times 10^9/\text{L}$, such children are at a slightly increased risk of bacteremia.^{2,3} Recommendations

generally suggest treatment with either amoxicillin or ceftriaxone. Ceftriaxone is favored by many practitioners because of its broad spectrum of activity and its long half-life. Is this approach reasonable?

Epidemiology

A helpful diagnostic approach is to first understand the epidemiology and natural history of occult bacteremia. Currently, in $>90\%$ of cases, bacteremia is caused by *Streptococcus pneumoniae*; in 3% to 5% of cases, by *Salmonella* species; and, rarely, by *Meningococcus*, *Staphylococcus aureus*, or other streptococci.⁴ *Haemophilus influenzae* B—formerly the second

most frequent cause of occult bacteremia and the leading cause of meningitis—has been nearly eliminated through vaccination. Before vaccination for *H influenzae* B was available, incidence of meningitis was estimated to be one case per 300 febrile children. Now that *H influenzae* B has been virtually eliminated, incidence of meningitis is estimated to be one case per 1000 to 1500 febrile children—a reduction of $>70\%$.⁵

**... in $>90\%$ of cases,
bacteremia is caused by
Streptococcus pneumoniae;
in 3% to 5% of cases,
by *Salmonella* species;
and, rarely,
by *Meningococcus* ...**

In comparison with that of *H influenzae* B, the natural history of *S pneumoniae*-related occult bacteremia is fairly benign. Spontaneous resolution of disease occurs in 85% to 90% of cases;⁶ and in 10% to 15% of cases, the result is secondary infection or persistent bacteremia (after >24 hours).⁷ Pneumonia, meningitis, osteoarthritis, and soft-tissue infection are the most common sites of secondary focal infection.⁴

Management

I will attempt to address three questions important for deciding on an approach to management of possible occult bacteremia:

1. *What is the risk of a bad outcome (ie, death or brain damage) in a child with occult bacteremia?*

Except for meningitis, all secondary infections caused by

S pneumoniae-related occult bacteremia result in generally good outcomes; and immunocompetent children almost never die of occult bacteremia. Unfortunately, however, meningitis develops in 2% to 3% of these children^{5,8} and causes clinically significant morbidity (30-40% neurologic morbidity) and mortality (about 5-10%).⁴ The risk of a bad outcome, therefore, is low (ie, one case per 2000-3000 febrile children).

2. *Do antibiotics reduce risk of secondary infection in *S pneumoniae*-related occult bacteremia?*

The answer to this question is yes. The rate of secondary infection in patients treated with antibiotic agents is reduced from a range of 10% to 15% (in untreated patients) to a range of 3% to 6% (in patients treated with oral or parenteral antibiotic agents, usually amoxicillin and ceftriaxone).^{1,4}

3. *Does use of antibiotic agents reduce risk of meningitis in patients with *S pneumoniae*-related occult bacteremia?*

This question is most important because bad outcomes (ie, death or brain damage) occur only with meningitis. Three metaanalyses^{5,8,9} have been published, including one⁹ supporting the contention that compared with no use of antibiotic therapy, use of antibiotic agents either orally (amoxicillin) or parenterally (ceftriaxone) decreases the risk of meningitis well and equally. A second study⁵ suggests a decreased trend toward meningitis in patients treated with oral antibi-

In our efforts to provide practical clinical information, we are introducing a new feature with this issue called *Corridor Consult*. We hope to give brief answers to specific common clinical questions. For those searching for further information on any topic covered, we will, wherever possible, provide links on our Web site: www.kp.org/permanentejournal to either the MEDLINE abstract or the original resource article in the reference section. The purpose of this feature is to help clinicians in their everyday practice. Those readers with suggestions of specific clinical questions to be answered or other comments can contact Scott Rasgon, MD, at *The Permanente Journal*, e-mail: permjournal@kpnw.org.



otics (2.7%) compared with the rate in patients who receive no treatment (0.8%), but this difference failed to reach statistical significance. A third study⁸ showed that rate of meningitis was identical whether antibiotic agents were administered orally or parenterally.

Conclusions and Recommendations

S pneumoniae accounts for occult bacteremia in >90% of children three months to three years of age; and this condition resolves spontaneously in 90% of affected children. Oral amoxicillin therapy or parenteral ceftriaxone therapy decreases rate of persistent bacteremia and secondary infection by about 60% to 70%. However, ceftriaxone is not superior to amoxicillin. Only one metaanalysis⁹ supports the conclusion that antibiotic therapy decreases rate of meningitis. Results of two additional metaanalyses^{5,8} suggest a decreased trend toward meningitis but failed to reach statistical significance. None of these studies show any difference in rate of meningitis among patients who receive oral antibiotic therapy with amoxicillin compared with patients who receive parenteral antibiotic therapy with ceftriaxone.

This information is probably all that we will ever know about occult bacteremia as we enter the era of Prevnar pneumococcal conjugate vaccine (Wyeth Lederle Vaccines unit of Wyeth-Ayerst Labora-

tories, Philadelphia, PA)—an era in which we will probably be able to reduce the rate of *S pneumoniae*-related occult bacteremia by about 90%. Before the advent of the *H influenzae* B conjugate vaccine, the incidence of meningitis was estimated to be one case per 300 febrile children of this age with temperature >39°C. Estimates suggest that if Prevnar is 90% effective, incidence of meningitis in the near future will be one case per 10,000 to 15,000 febrile children. We are on the verge of nearly eliminating meningitis in children; meningitis will increasingly be a disease seen mainly in adults.

We are on the verge of nearly eliminating meningitis in children; meningitis will increasingly be a disease seen mainly in adults.

Therefore, I believe that antibiotic treatment is unnecessary for febrile children at risk for occult bacteremia; however, health care practitioners who choose to administer antibiotic therapy will find that amoxicillin is as effective as ceftriaxone in these patients. ♦

References

1. Fleisher GR, Rosenberg N, Vinci R, et al. Intramuscular versus oral antibiotic therapy for the prevention of meningitis and other bacterial sequelae in young, febrile children at risk for

occult bacteremia. *J Pediatr* 1994 Apr;124(4):504-12.
2. Jaffe DM, Fleisher GR. Temperature and total white blood cell count as indicators of bacteremia. *Pediatrics* 1991 May;87(5):670-4.
3. Baraff IJ. Management of infants and children 3 to 36 months of age with fever without source. *Pediatr Ann* 1993 Aug;22(8):497-8, 501-4.
4. Kuppermann N. Occult bacteremia in young febrile children. *Pediatr Clin North Am* 1999 Dec;46(6):1073-109.
5. Rothrock SG, Harper MB, Green SM, et al. Do oral antibiotics prevent meningitis and serious bacterial infections in children with Streptococcus pneumoniae occult bacteremia? A metaanalysis. *Pediatrics* 1997 Mar;99(3):438-44.
6. Jaffe DM, Tanz RR, Davis AT, et al. Antibiotic administration to treat possible occult bacteremia in febrile children. *N Engl J Med* 1987 Nov 5;317(19):1175-80.
7. Bachur R, Harper MB. Reevaluation of outpatients with Streptococcus pneumoniae bacteremia. *Pediatrics* 2000 Mar;105(3 Pt 1):502-9.
8. Rothrock SG, Green SM, Harper MB, et al. Parenteral vs oral antibiotics in the prevention of serious bacterial infections in children with Streptococcus pneumoniae occult bacteremia: a metaanalysis. *Acad Emerg Med* 1998 Jun;5(6):599-606.
9. Baraff IJ, Oslund S, Prather M. Effect of antibiotic therapy and etiologic microorganism on the risk of bacterial meningitis in children with occult bacteremia. *Pediatrics* 1993 Jul;92(1):140-3.

I believe that antibiotic treatment is unnecessary for febrile children at risk for occult bacteremia...

The Great Task

Accomplish the great task by a series of small acts.

Tao Te Ching