Management of the febrile child without a focus of infection in the era of universal pneumococcal immunization

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Should strategies of management of invasive disease in the febrile child without focus of infection (occult bacteremia) be reconsidered in communities with universal immunization of infants with the conjugate vaccines for Haemophilus influenzae type b and Streptococcus pneumoniae (PCV7)? The incidence of occult bacteremia is likely to decrease with the virtual elimination of H. influenzae type b and vaccine serotype pneumococcal invasive diseases. The number of children with fever coming to physicians’ offices, however, is unlikely to change. The challenge of distinguishing the febrile child with invasive bacterial disease who requires aggressive therapy from the febrile child who has a viral infection and requires only symptomatic therapy will persist. The bacteriology of invasive disease in infants and young children in 2002 will include pneumococcal serotypes not in PCV7; serotypes in PCV7 that occur in the unimmunized, partially immunized or fully immunized child (vaccine failures); Neisseria meningitidis; Salmonella spp., group A Streptococcus, Staphylococcus aureus and Gram-negative enteric bacilli. Management plans published in the 1990s suggested an aggressive diagnostic approach to the febrile child 3 to 36 months old who was toxic or had a temperature of >39°C. Diagnostic tests included white blood cell counts, cultures of blood and urine and chest radiograph and lumbar puncture as indicated by clinical signs and administration of parenteral ceftriaxone. Although PCV7 was extraordinarily effective in prevention of serotype-specific invasive pneumococcal disease in clinical trials, pediatricians need to know whether the results based on 38 000 enrollees will be maintained as millions of children are immunized. In addition questions about change in serotype of pneumococci causing invasive disease (serotype switching), herd immunity and durability of protection after immunization need to be answered. Until more experience is available to answer these questions, the febrile child without focus of infection should be managed without consideration of immunization with PCV7. Evaluation of the organism (serotype) and the host (acute and convalescent sera) should be undertaken for each case of invasive pneumococcal disease in this era of universal pneumococcal immunization.

INTRODUCTION

The management of the febrile child without a focus of infection, occult bacteremia, has been a subject of controversy for decades. Radetsky1 noted that more than 300 articles on management of the febrile infant had been published in the 36 years beginning in 1960. Streptococcus pneumoniae is responsible for the vast majority of episodes of occult bacteremia. With the availability and demonstrated efficacy of the heptavalent conjugate pneumococcal vaccine (PCV7) in prevention of invasive pneumococcal disease, does the strategy for management of the febrile child who is immunized with PCV7 need to be reconsidered? The purpose of this article is to review the microbial changes that are likely to occur in the era of universal pneumococcal immunization and the implications of these changes for altering management strategies for the febrile child.

MICROBIOLOGY OF OCCULT BACTEREMIA

Bacteriology of occult bacteremia in the 1990s. The bacterial pathogens responsible for occult bacteremias before the introduction of the conjugate polysaccharide Haemophilus influenzae type b vaccine in 1990 and PCV 7 in 2000 included S. pneumoniae, Haemophilus influenzae type b (Hib), Neisseria meningitidis, group A Streptococcus, Staphylococcus aureus, Salmonella spp. and Gram-negative enteric bacilli (Fig. 1). S.
Although still uncommon the appearance of invasive disease caused by *H. influenzae* type a<sup>6</sup> and type f<sup>7</sup> suggests the possibility that non-b serotypes could replace Hib as a serious pathogen.

**Influence of the conjugate pneumococcal vaccine on the bacteriology of occult bacteremia.** The success of PCV7 in prevention of invasive disease caused by serotypes in the vaccine in the Northern California clinical trial<sup>8</sup> will likely be replicated as millions of children are immunized. There are data that suggest a herd effect; an average of 34% of all children younger than age 5 years were vaccinated in Northern California between October, 1995, and March, 2001; during this time period there was a 62.4% reduction in invasive disease among children younger than 5 years.<sup>9</sup> Although problems with vaccine supply occurred in the summer and fall of 2001, by December, 2001, 23 million doses of PCV7 had been distributed in the United States (M Boken, Wyeth Lederle Vaccines, personal communication). If the vaccine proves to be 97% effective for prevention of pneumococcal disease caused by serotypes in the vaccine in fully immunized children (as occurred in the clinical trial), there will be a substantial decrease in episodes of occult bacteremia. Nevertheless invasive pneumococcal disease will persist in infants: (1) disease will occur caused by serotypes not in the vaccine; (2) disease will occur caused by serotypes in the vaccine and represent vaccine failures; (3) some children will not have protective antibodies because they were unimmunized or incompletely immunized; (4) some children will not have protective antibodies because of immune deficits. The possibility of vaccine switching in immunized children exists, i.e. increased incidence of invasive disease caused by serotypes not in the vaccine. Alternatively there might be protection for serotypes not in the vaccine but related to vaccine serotypes. The results of the microbiologic studies of otitis media in Finnish children<sup>10</sup> identified a reduction in the frequency of episodes caused by serotypes that cross-reacted with those in the vaccine (serotypes 6A, 9N, 18B, 19A and 23A). However, there was also a 33% increase in serotypes not in the vaccine causing otitis media. Thus even though the PCV7 is likely to be very effective, the nonvaccine serotypes of pneumococcus (and the uncommon cases of vaccine serotypes of pneumococcus) will persist as the most frequent pathogen associated with occult bacteremia (Fig. 1).

**SHOULD THE MANAGEMENT OF INFANTS WITH FEVER WITHOUT SOURCE WHO ARE IMMUNIZED WITH PCV7 CHANGE?**

Fever without source in infants will continue to be a common cause of office visits to physicians. About two-thirds of children between the ages of birth and 2 years visit the physician for an acute febrile illness.<sup>11</sup>
Fever without source is the diagnosis in ~14% of office visits. Because the overall incidence of invasive disease among febrile infants was low, the introduction of the conjugate vaccines will not diminish the number of office visits for fever without source. The challenge to the practitioner of distinguishing the few children with invasive bacterial disease who require aggressive management from the many children who have presumably viral and spontaneously resolving disease that can be managed with symptomatic treatment will remain. The guidelines below are suggestions for current management of the infant with fever without source in the era of universal *Haemophilus* and pneumococcal immunizations.

**Management of the febrile neonate.** Fever in the first weeks of life is relatively uncommon. However, when fever does occur the incidence of severe disease including sepsis is sufficiently high to warrant careful evaluation and conservative management. Invasive disease caused by *S. pneumoniae*, *H. influenzae* (usually nontypable) and *N. meningitidis* occurs but is uncommon. Practice guidelines prepared by Baraff et al.² for management of febrile infants younger than 28 days suggest that all should be considered for hospitalization and parenteral antibiotic therapy unless there is a recognizable alternative and benign diagnosis. The differential diagnosis of fever in the first month of life includes five categories based on pathogenesis: *in utero* infections; infections acquired at delivery (early and late onset sepsis); infections acquired in the nursery; infections acquired in the household; and infections acquired because of underlying anatomic or physical disabilities (e.g. urinary tract infections). For presumed bacterial sepsis in the neonate, initial therapy with ampicillin and gentamicin continues to be appropriate.

**Management of the infant 29 to 90 days old with fever without source.** Invasive disease after the first month includes a mix of late onset disease associated with organisms acquired at delivery including group B streptococci, Gram-negative enteric bacilli and uncommonly *Listeria monocytogenes* and enterococci as well as the invasive organisms acquired in the household, pneumococci, meningococci and *H. influenzae*. Febrile infants in this age group may be categorized as toxic or nontoxic, and among the nontoxic group low risk or high risk for invasive bacterial disease.¹² Low risk criteria include: previously being healthy; having no focal bacterial infection on physical examination; and having negative laboratory screening. Negative laboratory screening is defined as a white blood cell (WBC) count of 5000 to 15 000/mm³, <1500 band forms/mm³, normal urinalysis, and when diarrhea is present, <5 WBC per high power field in stool. The percent of serious bacterial infections in infants 90 days of age or less by clinical and laboratory findings is 1.4% contrasted with 17.3% if the patients appears toxic. For the toxic or nontoxic but high risk patient, ceftriaxone (50 mg/kg once daily in the absence of meningitis) was recommended by Baraff et al.² and is still the regimen of choice. Parenteral ampicillin should be added for the rare cases of invasive disease caused by enterococci or *L. monocytogenes*. Because febrile infants in this age group would have received none or one dose of PCV7, the vaccine status of the child is irrelevant to therapeutic decisions.

**Management of the child 3 to 36 months of age with fever without source.** The risk of occult bacteremia in children 3 to 36 months of age without source was reported in the review of Baraff and colleagues to vary from 1.6 to 11% with a mean probability of 4.3% in children with a temperature of 39°C or more.²,¹² Bacteremia is more frequent in children with higher temperatures and elevated WBC counts. A summary of studies of WBC counts in children with fever without source by Baraff et al.² identified a mean probability of 2.6% in children with WBC <15 000 and 13% in children with WBC >15 000. Recent reports suggest that C-reactive protein has a better predictive value for occult bacteremia and serious bacterial infection than WBC counts.¹³

An algorithm for management of children 3 to 36 months of age with fever without source was proposed by Baraff et al.² and is frequently cited as a useful guide. Children who were toxic were hospitalized for sepsis workup and parenteral antibiotics; ceftriaxone 50 mg/kg/day in a single dose was recommended. Children who were not toxic but who had a temperature of 39°C or greater had WBC count; cultures of blood, urine and stool; and chest radiograph if clinical signs of lower respiratory tract infection were present. Empiric use of ceftriaxone was recommended for all children with temperature of 39°C or greater or for such febrile children if the WBC count was >15 000. These guidelines generated much discussion, and viewpoints varied among experts.¹⁴–¹⁶ Some argued that the expense and pain for the child of diagnostic tests and parenteral therapy were unwarranted because the incidence of invasive bacterial disease was low and many of the episodes of pneumococcal and *Haemophilus influenzae* bacteremia cleared without use of antimicrobial agents. Other experts countered that the role of the physician was as “gatekeeper” to protect the previously healthy child from the uncommon invasive event that had potential serious outcomes and that treating many to protect the few with severe disease was warranted. The purpose of this article is not to reconcile these viewpoints but to question whether or not the introduction of the conjugate pneumococcal vaccine alone warrants a change in the concepts of management of children who are fully immunized and have fever without source.
The history of vaccine safety and efficacy after approval and recommendations by authoritative groups is replete with surprises, most of which are unanticipated adverse events. The most recent example is the unexpected increased incidence of intussusception associated with rotavirus vaccine. PCV 7 had an excellent safety record during the clinical trials, but physicians still need to be alert for the rare adverse event that may be identified only after hundreds of thousands of children are immunized. The efficacy documented in the clinical trials must be corroborated as millions of children are immunized. In addition questions about the possibility of serotype switching, incidence of non-vaccine serotypes causing invasive disease and duration of protection will be answered only after sufficient experience has accumulated. For all these reasons the strategy of management of the child with fever without source should be the same irrespective of the history of PCV immunization. With the passage of time and greater experience, we can reassess these recommendations and consider change as directed by the data.

Careful and skilled observation remains the key to management of the febrile child. The key to management decisions of the febrile child without source remains the ability of the physician/nurse to distinguish the child who is toxic from the child who is not toxic; to distinguish the child who has altered affect including decreased state of alertness, decreased responsiveness, has difficulty in being consoled from the child who is playful, responsive, maintains eye contact and is readily consoled. The art of pediatrics, the powers of observation of the astute clinician, remains the key to management of the febrile child. The febrile illness is dynamic; the child will appear different, for better or worse, hours after the office visit. The physician needs to maintain contact with the family until the clinical episode is resolved. Selected laboratory tests, particularly WBC counts and differential, are of value if there is ambiguity in the clinical diagnosis, but if the test is performed the physician must respond to the results. None of these clinical issues changes in the era of universal pneumococcal immunization.

RESPONSIBILITY OF THE PHYSICIAN IN ASSESSING THE CHILD WITH PNEUMOCOCCAL BACTEREMIA

Physicians will continue to encounter children with episodes of invasive pneumococcal disease. To further document the efficacy of PCV 7 as millions of doses are administered to infants throughout the United States, thorough evaluation of each child with invasive pneumococcal disease will be necessary. The physician responsible for such a child should consider the following steps: (1) document the history of immunization with PCV 7 or pneumococcal polysaccharide vaccine: include dates of immunization, source of the vaccine and lot number; (2) obtain the pneumococcal isolate and submit for serotyping and susceptibility tests; (3) obtain acute and convalescent samples of blood: the acute serum will provide information about protective antibody at the onset of disease and whether or not the child responded to PCV 7 (if received). The convalescent serum will provide information about the ability of the patient to respond to the disease causing strain.

If the child has had prior episodes of pneumococcal disease or syndromes suggesting pneumococcal disease, an assessment of immune functions should be considered.

The Centers for Disease Control and Prevention has established a report form for tracking cases of invasive pneumococcal disease among vaccinated children. The instruction sheet and case report form can found at www.cdc.gov/nip.

SUMMARY AND CONCLUSIONS

(1) Fever without source will continue to be a frequent reason for visits to physicians. (2) The microbiology of occult bacteremia will likely change in the era of universal pneumococcal conjugate vaccine immunization. Nevertheless pneumococcal disease caused by serotypes not in the vaccine, due to vaccine failure or occurring in children who were not immunized or partially immunized or have immune defects will continue to be the most frequent cause of occult bacteremia. The incidence of meningococcemia or bacteremia caused by group A Streptococcus, Salmonella, Staphylococcus aureus or Gram-negative enteric bacilli will likely continue at recent rates of disease unless changes in the ecology of the pathogen occurs. (3) Fever in the infant to 28 days of life should be aggressively managed as in the past. (4) Fever in the first 3 months of life should be aggressively managed. Because the infant will have received at a maximum one dose of PCV 7, vaccine history is irrelevant to management decisions. (5) Management of the febrile infant without source of infection during ages 3 months to 3 years should not be changed until more extensive experience with PCV 7 is available. The history of vaccines is replete with surprises, and it is still too early in our understanding of the safety and efficacy of PCV 7 to warrant a change in strategy of the uncommon but potentially severe consequences of invasive bacterial disease in the occult bacteremia syndrome.

REFERENCES