Bacterial Meningitis Post–PCV7

Declining Incidence and Treatment

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Abstract: The epidemiology of bacterial meningitis in the United States has changed tremendously in the past 20 years. Since the introduction of the *Haemophilus influenzae* type b vaccine in 1988, the incidence of *H. influenzae* type b meningitis has declined by at least 97%, and *Streptococcus pneumoniae* has emerged as the most common etiologic agent. The PCV7 (7-valent pneumococcal conjugate vaccine [Prevnar]; Wyeth Pharmaceuticals) vaccine, which targets 7 pneumococcal serotypes, was introduced in 2000 and has had an enormous impact on both the incidence and epidemiology of bacterial meningitis. This article reviews the impact of the PCV7 vaccine and the most up-to-date evidence on diagnosis and empiric therapy of suspected bacterial meningitis in the current day.

Key Words: bacterial meningitis, PCV7, Prevnar, diagnosis, management

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TARGET AUDIENCE

This CME activity is intended for physicians, nurse practitioners, and nurses who care for children in an emergency setting.

LEARNING OBJECTIVES

After completion of this article, the reader should be able to:

1. Identify the current epidemiology of bacterial meningitis in various age groups.
2. Implement an evidence-based approach to empiric therapy for suspected bacterial meningitis.

BACTERIAL MENINGITIS

Bacterial meningitis is an infection-mediated inflammation of the pia, arachnoid, and subarachnoid space. Most children with meningitis who present to emergency departments in the current day have aseptic meningitis, but when bacterial etiology is suspected, diagnosis and therapy should be undertaken on an emergent basis. Even with optimum treatment, mortality in children is about 4%.[1] Neurologic sequelae are relatively common in survivors of meningitis, particularly after pneumococcal meningitis.[2–4]

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This CME article will describe the impact of PCV7 on the incidence of pneumococcal meningitis and the current epidemiology of bacterial meningitis in several age groups, as well as show clinicians how to use an evidence-based approach to empiric therapy for suspected bacterial meningitis.

HISTORICAL BACKGROUND

The epidemiology of bacterial meningitis in the United States has changed tremendously in the last 20 years. Before 1988, when conjugate vaccine against *Haemophilus influenzae* type b (Hib) became available in the United States, Hib accounted for 70% of bacterial meningitis in children younger than 5 years.[5] As a result of routine immunization, the incidence of Hib meningitis has declined by at least 97%, from 41 to 1.3 cases per 100,000 children over the period from 1987 to 1997.[6] *Streptococcus pneumoniae* then emerged as the most common etiologic agent of bacterial meningitis.

In response to the increased proportion of bacterial meningitis caused by *S. pneumoniae*, a heptavalent protein-polysaccharide conjugate vaccine was developed and licensed for use in infants and young children in the United States in February 2000. The 7-valent pneumococcal conjugate vaccine (PCV7) targets 7 pneumococcal serotypes: 4, 6B, 9V, 14, 18C, 19F, and 23F, which together cause 83% of invasive disease in children younger than 4 years.[7] The Advisory Committee on Immunization Practices recommended routine administration of PCV7 to children younger than 23 months, as well as to children 24 to 59 months who are at high risk of invasive disease.[8]

IMPACT OF PCV7 ON RATES OF PNEUMOCOCCAL DISEASE

A vaccine efficacy trial performed in the Kaiser Permanente network before the vaccine's release showed 97.4% efficacy in preventing invasive disease caused by any of the 7 serotypes in fully vaccinated children versus controls (95% confidence interval [CI], 82.7%–99.9%). Efficacy against any of the 90 existing pneumococcal serotypes after at least 1 dose of PCV7 was 89.1% (95% CI, 73.7–95.9). Of note, the vaccine was 7% effective in preventing episodes of otitis media[7] and 30.3% effective in preventing first episode of radiographically confirmed pneumonia.[9]

Since the time of its licensure, the PCV7 vaccine has had a significant impact on rates of pneumococcal disease. The Active Bacterial Core, a component of the Centers for Disease Control and Prevention Emerging Infections Programs Network (ABC CDC), reviewed laboratory trends in 8 regions of the United States and found that rates of pneumococcal meningitis fell 62% in children 2 to 23 months old, and 34% in children 2 to 10 years of age from 1998 to 2007.[10] Invasive disease, defined as isolation from a normally sterile site, dropped from 24.3 to 17.3 cases per 100,000 from 1998 to 2001. The most positively impacted group was children younger than 2 years, in whom rates dropped from 188 to 59 cases per 100,000—a decrease of 69% overall.[11]

The network noted a concerning trend: despite the overall decline in incidence of pneumococcal meningitis, rates of non–PCV7-serotype meningitis have increased significantly by 61% overall and by 92% among children younger than 5 years, representing an increase from 0.87 to 1.67 cases per 100,000 persons in that age group from 1998 to 2007.[10]

Other groups have had similar findings. From 1994 to 2002, The US Pediatric Multicenter Pneumococcal Surveillance Group noted a rise in the proportion of isolates that were non-PCV7 serotypes, from 6% to 37.6% in children younger than 2 years.[12]

The long-term effects of this changing profile in the causative serotype for invasive disease are not yet known.

EMERGING SEROTYPES

Certain nonvaccine serotypes, particularly 19A and 22F, have emerged as more prevalent than their counterparts. The ABC CDC Network found that disease due to serotype 19A increased from 0.02 to 0.08 cases per 100,000 children, and disease due to serotype 22F increased from 0.03 to 0.08 per 100,000 children from 1998 to 2005.[13]

The US Pediatric Multicenter Pneumococcal Surveillance Group had similar findings. In their multicenter study, meningitis cases due to serotype 19A increased from 5 cases (1.5% of total cases) to 28 cases (11.1% of total cases) from 1994 to 2002. Cases due to serotype 22F increased from 2.4% to 10.3% of total cases.[12]

The increasing prevalence of serotype 19A is particularly worrisome in light of its poor susceptibility to penicillin. The ABC CDC Network found that 60.7% of isolates from persons with meningitis showed decreased penicillin susceptibility. Comparatively, other non-PCV7 isolates showed decreased susceptibility only 12.4% of the time.[13]

PCV13

PCV13 (Prevnar 13; Wyeth Pharmaceuticals) was licensed by the Food and Drug Administration in February 2010 and contains all capsular polysaccharides found in PCV7, as well as serotypes 1, 3, 5, 6A, 7F, and 19A.[14] These 6 additional serotypes were selected on the basis of their increasing prevalence in the post-PCV7 era; as of 2007, they accounted for 63% of invasive pneumococcal disease.[15] Controlled trials have demonstrated an adverse effect profile that is similar to that of PCV7.[16] The American Academy of Pediatrics Committee on Infectious Diseases recommended PCV13 as a replacement for PCV7 in the standard childhood vaccination schedule, and schedules for standard and catch-up dosing have been published.[14] PCV13 has the potential to even further reduce the incidence of pneumococcal meningitis.

EPIDEMIOLOGY OF BACTERIAL MENINGITIS

Streptococcus pneumoniae remains the most common cause of bacterial meningitis in children outside the neonatal period, followed by *Neisseria meningitidis*. A retrospective review of children presenting to 20 US pediatric centers between 2001 and 2004 described the etiology of 231 cases of bacterial meningitis.[17] The most common pathogens by age group were as follows:

- 1 to 3 months: *Streptococcus agalactiae* (39%), gram-negative rods (32%), *S. pneumoniae* (14%)
- 3 months to 3 years: *S. pneumoniae* (45%), *N. meningitidis* (34%), *S. agalactiae* (11%)
- 3 to 10 years: *S. pneumoniae* (47%), *N. meningitidis* (32%)
- 10 to 19 years: *N. meningitidis* (55%), *S. pneumoniae* (21%)

A recent multicenter study had similar findings. Group B streptococcus was the most common causative agent (86%) in children younger than 2 months, *N. meningitidis* (46%) in children 11 to 17 years, and *S. pneumoniae* in all other pediatric age groups.[10]

Certain factors also suggest specific pathogens. For example, common pathogens in basilar skull fracture are *S. pneumoniae* and *H. influenzae*. In the presence of a cerebrospinal fluid (CSF) shunt, penetrating head trauma, or recent neurosurgery, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa* should be considered.[18] Host immune defects should also be taken into consideration. Absence of opsonizing antibody is associated with *S. pneumoniae* and *H. influenzae*, complement deficiency with *N. meningitidis*, and HIV infection with *Cryptococcus neoformans*, *S. pneumoniae*, and *Listeria monocytogenes*.[19]

Neonates are particularly susceptible to bacterial meningitis. Whereas incidence has declined in all other age groups, it has not done so in children younger than 2 months, with 73 cases per 100,000 in 1998 and 81 per 100,000 in 2007.[10]

HISTORY AND PHYSICAL EXAMINATION

Signs and symptoms of meningitis depend on patient age, host response to infection, and the point in time at which the patient is evaluated. In its earliest stages, signs of meningitis may be quite subtle, making it difficult to distinguish from other infections.

The older child with meningitis may have a history of fever, headache, photophobia, vomiting, seizure, or changes in mental status such as lethargy or irritability. Infants with meningitis may present with less specific signs, such as fever, hypothermia (<1 month of age), vomiting, or poor feeding. Parents may describe paradoxical irritability, in which infants become more irritable with attempts at consolation. The clinician should also ascertain immunization status, drug allergies, any history of recent antibiotic use, and predisposing factors such as recent respiratory or otic infection, cochlear implant devices, and anatomic defects such as dermal sinus or urinary tract abnormalities, which can predispose to gram-negative meningitis.[20]

The physical examination should be directed at an assessment of volume status, the presence of shock, neurologic deficits, neck stiffness, and signs of increased intracranial pressure. Neck stiffness and other meningeal findings, such as Kernig and Brudzinski sign, are not reliably elicited in children younger than 2 years. Cutaneous findings may include petechiae or purpura. Infants may present with a bulging fontanelle.

Lyme meningitis should be considered in endemic areas during the summer and early fall, particularly if erythema migrans or cranial nerve palsy is present.[21]

Most studies of the history and physical in diagnosing bacterial meningitis were published in the pre-PCV7 era.[22–25] In 2008, Nigrovic et al[17] retrospectively described the presentation of bacterial meningitis in 231 children aged 29 days to 19 years who presented to 20 US emergency departments between 2001 and 2004. About one-third had been pretreated with antibiotics. They found that 7% of children were afebrile, 73% had been febrile within 72 hours of presentation, and 20% had been febrile for greater than 72 hours. Ten percent had a seizure at or before the time of presentation. Thirteen percent had severely altered mental status. Regarding physical findings, 40% had meningismus, and 4% had purpura.[17]

LABORATORY EVALUATION

Approach

Cultures of the CSF and peripheral blood should be obtained as expediently as possible—preferably before the initiation of antibiotics. If the patient is hemodynamically unstable, or requires computed tomography (CT scan) before lumbar puncture, then antibiotics may be started after a blood culture is obtained.[18] Because the results of CSF and blood cultures are typically not available in the emergency department, preliminary studies such as peripheral white blood cell (WBC) count with differential and CSF glucose, protein, cell count with differential, and Gram stain should be obtained to help confirm the diagnosis of bacterial meningitis. Peripheral blood electrolytes, glucose, and coagulation studies should be obtained to guide supportive therapy. Viral testing should also be considered where available.

Cerebrospinal Fluid

Cytology

The CSF WBC count in bacterial meningitis is typically elevated, measuring 1000 to 5000 WBCs/μL, with a range of less than 100 to 10,000 WBCs/μL.[18] However, it is important to note that in the post-PCV7 era, most children with CSF pleocytosis do not have bacterial meningitis. A multicenter study of children aged 29 days to 19 years found that, after excluding pretreated patients, only about 4% of children with CSF pleocytosis ($\geq 10 \times 10^6$ cells/L) had bacterial meningitis. The remainder were presumed to have aseptic meningitis.[26]

Little has been written about CSF parameters in the newborn patient during the post-PVC7 era. One study[27] found a median of 3 WBCs/μL (95th percentile = 19 WBCs/μL) in the CSF of normal, healthy neonates aged 0 to 28 days without bacterial meningitis, or other conditions that might cause CSF pleocytosis. The median for children 29 to 56 days was 2 WBCs/μL (95th percentile = 9 WBCs/μL).

Bacterial meningitis typically results in a predominance of neutrophils (80%-95%) in CSF, although about 10% of patients present with greater than 50% lymphocytes or monocytes.[18] It should be noted that the presence of neutrophils in the CSF, although considered abnormal,[22,23] is not entirely specific for bacterial disease; patients with aseptic meningitis may also have neutrophils in their CSF.[22]

Immature neutrophils (bands) were found to be present in the CSF of 29% of patients with bacterial meningitis and 18% of those with aseptic meningitis.[26]

A traumatic lumbar puncture can cause bleeding into the CSF, interfering with interpretation of the CSF cell count. Although the ratio of red cells to white cells in a traumatic puncture usually falls in the range of 500:1 to 1000:1, no formula can be used with total confidence to exclude meningitis.[28] Therefore, in the event of a traumatic lumbar puncture when the interpretation of the ratio is uncertain, the patient should be treated presumptively for bacterial meningitis until the results of the CSF culture become available. In many cases (eg, CSF with 50,000 red blood cells/μL and 12 WBCs/μL); however, the WBCs can be clearly attributed to trauma from the procedure, and antibiotic treatment is unnecessary.

Chemistry

Cerebrospinal fluid glucose in bacterial meningitis is typically less than 40 mg/dL, with a depressed ratio of CSF to blood glucose, usually 0.4 or less (or ≤0.6 in term neonates).[18]

Cerebrospinal fluid protein is typically elevated, ranging from 100 to 500 mg/dL.[29] A recent study of traumatic lumbar puncture suggests that CSF protein should be corrected (decreased) by 1.1 mg/dL for every 1000 CSF red blood cells.[30]

Microbiology

The presence of an organism on CSF Gram stain suggests a bacterial etiology. One retrospective study of the test characteristics of Gram stain in patients younger than 21 years found a sensitivity of 67% and specificity of 99%. However, 40% of positive Gram stains were falsely positive, and a small percentage (21/17,499 = 0.1%) were falsely negative.[31] Nigrovic et al[32] calculated a similar sensitivity (72%), although when logistic regression was performed, a positive Gram stain was the best predictor of bacterial meningitis. Results of Gram stain should be interpreted judiciously on a case-by-case basis.

Cerebrospinal fluid culture, when positive, confirms the diagnosis of bacterial meningitis. However, a negative culture does not preclude infection. In a study of children with bacterial meningitis, CSF cultures were positive in 97% of those who had not been pretreated, 67% of those who had received oral antibiotics, and 56% of those who had received intravenous (IV) antibiotics before undergoing lumbar puncture.[33]

Cerebrospinal fluid bacterial antigen detection tests are not recommended for routine use because they have not been shown to significantly modify physician decision making,[34] and because false-positive tests have been reported.[35] Some authors recommend that they be reserved for cases in which patients have been pretreated with antibiotics.[18] This recommendation is based largely on a study[36] that found that 25% of pretreated patients had a negative CSF culture but a positive CSF bacterial antigen test.

Peripheral Blood

Nigrovic et al,[17] during the post-PCV7 era, found that the peripheral WBC count in children with bacterial meningitis ranged from 8.3 to 22.3 cells $\times 10^3$/μL, with a mean of 15.1 cells $\times 10^3$/μL. Peripheral bandemia was noted in 75% to 100% of cases of bacterial meningitis, but was also present in 14% to 80% of aseptic meningitis cases,[26] making bandemia a poor marker for bacterial disease.

EFFECT OF PRETREATMENT ON CSF FINDINGS

It is not uncommon to care for a child with suspected meningitis who has received antibiotics before lumbar puncture. This may occur in a patient who has been receiving oral antibiotics, was transferred from an outside center, required CT scan before lumbar puncture, or was not deemed hemodynamically stable for lumbar puncture. In this case, the interpretation of CSF can be challenging.

In a large, retrospective post-PCV7 era study,[37] prior administration of antibiotics (defined as antibiotics within 72 hours of lumbar puncture) in children ultimately diagnosed with bacterial meningitis was associated with increased CSF glucose concentration and decreased CSF protein concentration compared with nonpretreated children. The rate of positive CSF cultures fell from 84% in the nonpretreated group, to 72% in those who had been treated for less than 4 hours, 55% in those treated for 4 to 11 hours, and 58% in those treated for more than 12 hours. However, CSF WBC count and neutrophil count were not significantly affected.

A study from the pre-PCV7 era[33] looked specifically at the effect of a parenteral third-generation cephalosporin on sterilization of CSF cultures, by pathogen. Sterilization of CSF was

most rapid in children with meningococcal meningitis—3 of 9 children had sterile CSF within 1 hour of treatment, and all CSF specimens were sterile by 2 hours. For *S. pneumoniae*, the first negative culture was obtained at 4 hours, and 5 of 7 were negative by 10 hours. In the case of *S. agalactiae*, the first negative culture was obtained at 24 hours.

In general, CSF interpretation in the pretreated patient should be undertaken with an emphasis on the WBC count and neutrophil count, which are least likely to normalize with therapy.

LUMBAR PUNCTURE AND RISK OF HERNIATION

Concern is commonly expressed about the risk of cerebral herniation when performing lumbar puncture in a patient with potentially increased intracranial pressure. Even in infants with an open fontanelle, the theoretical possibility of herniation exists, if the pressure gradient between the intracranial cavity and subarachnoid space is sufficient. Although controlled studies are not likely to be undertaken in this area, case reports suggest that herniation is unlikely unless the patient is unresponsive to pain or has fixed or dilated pupils, abnormal respirations, or abnormal posture.[38,39] The IDSA (Infectious Diseases Society of America) guideline for the management of bacterial meningitis, published in 2004, states that CT scan should be completed before lumbar puncture in patients with immune compromise, ventricular shunts, hydrocephalus, CNS trauma, recent neurosurgery, known space-occupying lesion, papilledema, or a focal neurologic deficit with the exception of cranial nerve VI and VII palsy.[18] It should be noted that a normal CT scan cannot absolutely preclude herniation during lumbar puncture.[40]

DISTINGUISHING BACTERIAL FROM ASEPTIC MENINGITIS

The Bacterial Meningitis Score

Because of the high morbidity and mortality associated with untreated bacterial meningitis, patients with CSF pleocytosis are often admitted to the hospital for empiric antibiotic therapy until results of the CSF culture become available. This practice can lead to unneeded hospital admissions and receipt of broad-spectrum antibiotics. Multiple scoring systems have been devised to help distinguish between bacterial and aseptic meningitis. However, even the most recent models are based on data from the pre-PCV7 era.[41] One such score, the Bacterial Meningitis Score (BMS),[32] was validated on a post-PCV7 cohort[42] and will therefore be the focus of this discussion. The study population was composed of children with CSF pleocytosis (defined as >7 WBCs/μL; changed to >10 WBCs/μL for the validation cohort) who were not critically ill or immune suppressed and had not received antibiotics in the preceding 72 hours. Recursive partitioning was used to identify the 5 best predictors of bacterial meningitis, as follows:

- positive CSF Gram stain
- CSF protein 80 mg/dL or greater
- CSF neutrophils 1000 cells/μL or greater
- peripheral ANC 10,000 cells/μL or greater
- seizure before or at the time or presentation

A BMS of zero was found to correspond to "low risk" for bacterial meningitis, with a negative predictive value of 100% (95% CI, 97%–100%). Validation was undertaken in a post-PCV7 cohort[42] of 2903 children 29 days to 19 years of age. In this cohort, a BMS of zero also had a high negative predictive value, at 99.9% (95% CI, 99.6%–100%). Two of 1714 patients categorized as low risk (scoring 0) actually had bacterial meningitis. Both patients were younger than 2 months and were infected with *Escherichia coli*. Based on these results, it is reasonable to use the BMS in children older than 2 months to identify those at low risk for bacterial meningitis, who could be safely managed as outpatients.

Enteroviral Polymerase Chain Reaction

Rapid detection of enteroviruses by polymerase chain reaction (PCR) is an emerging technique that may be helpful in establishing the diagnosis of enteroviral meningitis, a common form of aseptic meningitis. Polymerase chain reaction is more sensitive than viral culture for enterovirus, with sensitivity 86% to 100% and specificity 92% to 100%.[43] Polymerase chain reaction also provides prompt results (within 3 hours where available) and, when positive, has been shown to reduce the duration of IV antibiotic therapy as well as length of stay.[44] In a recent study, no child with CSF pleocytosis and a positive enteroviral PCR had concomitant bacterial meningitis, suggesting that such children might be safely treated as outpatients if they are otherwise well appearing.[45]

Biomarkers

Multiple biomarkers have been assessed for their ability to distinguish between bacterial and aseptic meningitis.[46–48] The most promising of these is serum procalcitonin,[49] using a cutoff of 0.5 ng/mL. The largest and most recent study of procalcitonin in children found a sensitivity of 99% and a specificity of 83% for distinguishing bacterial from viral meningitis. However, the study centers were in 6 different European countries, all of which documented universal Hib vaccination, but did not mention rates of vaccination against *S. pneumoniae*. Further investigation is required before incorporating procalcitonin into routine clinical decision making.

EMPIRIC THERAPY

Immediate therapy of presumed bacterial meningitis includes monitoring and stabilization of ventilation and perfusion, at the same time as IV access and laboratory studies are obtained. If septic shock is present, isotonic IV fluids should be administered. In the euvolemic patient, moderate fluid restriction is appropriate, especially in the setting of hyponatremia. Hypoglycemia, acidosis, and coagulopathy should be treated if present.

Ideally, a culture of the CSF should be obtained before initiating antibiotic therapy. However, when hypotension and/or end organ failure is present, administration of antibiotics takes precedence. In such cases, every attempt should be made to obtain a blood culture before antibiotics are given.

Empiric antibiotic therapy is based on 2 premises. First, because the CSF is a site of impaired humoral immunity, the agent must be bactericidal against the infecting organism.[50,51] Second, the agent must be able to cross the blood-brain barrier and reach sufficient concentration in the CSF, keeping in mind that peak concentration of drugs in CSF increases with inflammation of the blood-brain barrier.[52] In general, empiric therapy should be with IV rather than oral antibiotics, because the tissue levels achieved tend to be higher.

Choice of therapeutic agent should be based on the most likely pathogen, local susceptibility patterns, and additional risk factors. The IDSA guidelines for empiric therapy are as follows[18]:

Younger Than 1 Month

Neonates should be covered for *S. agalactiae*, *E. coli*, and *L. monocytogenes* with ampicillin plus either cefotaxime or an

aminoglycoside.[18] In addition, empiric acyclovir therapy for herpes simplex virus should be considered, particularly as delayed therapy of neonatal herpes simplex virus disease has been associated with increased mortality.[53] It is generally accepted that acyclovir should be started in those febrile neonates with rash, seizure, maternal history, or ill appearance. There is no consensus regarding therapy for febrile infants who are otherwise well.[54–56]

Older Than 1 Month

Vancomycin plus a third-generation cephalosporin (ceftriaxone or cefotaxime) should be used as empiric coverage of *S. pneumoniae*, including cephalosporin-resistant strains, and *N. meningitidis*, including penicillin-resistant strains.

Of note, *N. meningitidis* has demonstrated penicillin nonsusceptibility rates as high as 30.2% in North America.[57] Although the majority of nonsusceptible strains demonstrate intermediate, rather than complete, resistance[58–60] and remain sensitive to high-dose penicillin,[61] ceftriaxone is still indicated as empiric therapy of suspected or culture-proven meningococcal disease until sensitivity results are known.[18]

Ceftriaxone also provides coverage of *H. influenzae* in the event that the patient is unimmunized or from a developing country that does not routinely immunize against Hib.

Role of Rifampin

Some experimental literature has addressed the role of rifampin, rather than vancomycin, in conjunction with ceftriax one. Rifampin appears to have reliable CSF penetration in children[62] and, if given before ceftriaxone, may result in less exuberant release of inflammatory mediators during bacterial lysis, possibly attenuating treatment-related neuronal damage.[63] Some experts already recommend the substitution of rifampin for vancomycin when dexamethasone has been given.[18] Additional trials are needed before this substitution becomes universal practice.

Children With Predisposing Factors

The IDSA guidelines for children with specific predisposing factors are listed in Table 1.[18]

Antimicrobial Resistance

The first drug-resistant pneumococcal strain was reported in 1967,[64] and the incidence of drug-resistant pneumococcal disease increased steadily over the next decades.[65] However, because antibiotic resistance occurs most commonly in those serotypes that cause invasive disease,[12] these serotypes were naturally included in the PVC7 vaccine. Therefore, although the proportion of disease caused by drug-resistant strains appears to have remained constant over time, a significant decline in the incidence of resistant disease has occurred, mirroring the significant decline in the incidence of disease overall.

Between the years 1998/1999 and 2004/2005, the ABC CDC Network found that the incidence of penicillin nonsusceptibility in pneumococcal meningitis fell from 0.32 to 0.19 cases per 100,000 at-risk persons, a decline of 41.1%. In children younger than 2 years, the decline was more pronounced at 64.8%. Over the same period, the incidence of cefotaxime nonsusceptibility fell by 60% overall and 78.4% in children younger than 2 years.[10]

Although the decline in nonsusceptibility appears encouraging, antibiotic resistance remains an important issue in the empiric therapy of meningitis. Overall, in 2005, the percentages of pneumococcal isolates causing meningitis that had intermediate susceptibility and complete resistance to penicillin were 17.5% and 9.9%, respectively; to cefotaxime, 6.3% and 2.8%; and to meropenem, 4.0% and 7.5%. All isolates were sensitive to vancomycin.[10]

THE ROLE OF CORTICOSTEROIDS

Animal models have shown that the inflammatory response is a key factor contributing to morbidity and mortality in bacterial meningitis. Corticosteroids as adjunct therapy have been extensively studied because they have the potential to mediate this inflammatory response, thereby decreasing cerebral edema, intracranial pressure, and subsequent neuronal injury.[66,67] However, studies of corticosteroids in children with bacterial meningitis have not shown consistently positive results.

Based on the best available evidence, the American Academy of Pediatrics Committee on Infectious Diseases suggests that dexamethasone therapy may be useful in children with Hib meningitis if given concomitant with, or before, the first dose of antibiotics, but is unlikely to provide benefit if administered more than 1 hour after antibiotics have been given. Steroids may be considered for infants and children older than 6 weeks with pneumococcal meningitis after considering the risks and benefits.[68] In general, as the incidence of Hib meningitis has so dramatically decreased, steroids are unlikely to be beneficial for children with bacterial meningitis in the post-PCV7 era.

Pre-PCV7 Studies

Randomized controlled trials in children from the pre-PCV7 era[69–79] were summarized in a 1997 meta-analysis by McIntyre et al.[80] Most patients (62%) were infected with Hib meningitis. The authors found no effect of dexamethasone on

TABLE 1. IDSA Guidelines for Children With Specific Predisposing Factors

Predisposing Factor	Likely Pathogens	Empiric Therapy
Basilar skull fracture	*S. pneumoniae*, *H. influenzae*, *Streptococcus pyogenes*	Vancomycin + third-generation cephalosporin
Penetrating trauma or recent neurosurgery	*S. aureus*, *S. epidermidis*, *P. aeruginosa*	Vancomycin + cefepime, ceftazidime, or meropenem
Ventricular shunt*	*S. epidermidis*, *P. aeruginosa*, *Propionobacterium acnes*	Vancomycin alone; if Gram stain reveals the presence of gram-negative bacilli, then add cefepime, ceftazidime, or meropenem

*In place for more than 3 months. Otherwise, see recommendation for recent neurosurgery.

child mortality. Dexamethasone was highly protective against hearing loss for patients infected with Hib. For those infected with *S. pneumoniae*, there was a nonsignificant protective trend against hearing loss, which became significant when only those studies of early dexamethasone administration (dexamethasone given before or with the first dose of antibiotic) were considered. Steroids had no clear benefit for neurologic deficits other than hearing loss.

Three recently published studies were also conducted during the pre-PCV7 era.[81–83] Two of these specifically studied children with pneumococcal meningitis. McIntyre et al[82] performed a retrospective study of 120 pediatric cases identified via laboratory surveillance in Australia. They found that steroids administered with or before antibiotics were significantly associated with lower mortality rates. However, time until death was not reported; therefore, it is unclear whether some deaths might have been attributable to complications of a prolonged hospital stay rather than to lack of steroids. Ozen et al[81] performed a retrospective study of 55 pediatric cases identified in hospital archives in Turkey. They described no difference in IQ scores or other neuropsychological test results between those who had and had not received steroids; however, those children who had received dexamethasone had significantly better academic performance when measured in 3 tiers (awarded certification for high scores, failed at least 1 grade, and average). The school failure rate was also higher in those who had not received dexamethasone (56% vs 19%).

PCV7-Era Studies

A recent Cochrane meta-analysis[84] included 10 studies from the series of McIntyre et al and added 2 large pediatric series,[85,86] one from the post-PCV7 era.[86] In this meta-analysis, 38% and 35% of all patients were infected with Hib and *S. pneumoniae*, respectively. There was no effect of steroids on child mortality, with a risk ratio (RR) of 0.99 (95% CI, 0.91–1.20). There was a significant protective effect against hearing loss for children infected with Hib, with a RR of 0.37 (95% CI, 0.20–0.68). There was no protective effect for non-Hib species, RR = 0.86 (95% CI, 0.57–1.3).

At the time of this publication, we are aware of only 1 study of steroids and mortality in bacterial meningitis in children, with data collected in the United States in the post-PCV7 era. This retrospective cohort study by Mongelluzo et al[1] included 2780 children identified through the Pediatric Health Information System's administrative database. They found that adjuvant corticosteroid therapy had no effect on mortality or time to hospital discharge, regardless of age or infecting pathogen.

Studies in Neonates

There is a paucity of data regarding the use of corticosteroids in neonatal bacterial meningitis. One small study[87] showed no statistical difference in mortality, with 22% and 28% in the dexamethasone and control groups, respectively. Neurologic sequelae were described in 30% and 39% of patients, respectively. There are still insufficient data to make a recommendation on the use of corticosteroids in neonates with suspected bacterial meningitis.

OTHER ADJUNCT THERAPY

Although dexamethasone is the only extensively studied adjunct therapy for bacterial meningitis, several experimental agents are also under investigation. Glycerol therapy significantly reduced severe neurologic sequelae in a Latin American study of children with bacterial meningitis.[83] In another study conducted in Finland, glycerol was more effective than dexamethasone in preventing neurologic sequelae.[78]

Other anti-inflammatory agents studied include nonsteroidal anti-inflammatory drugs such as ketorolac,[88] monoclonal antibody against tumor necrosis factor α,[89] and labradimil.[90]

SUMMARY

In summary, *S. pneumoniae* is the most common etiologic agent of bacterial meningitis in children outside the neonatal period. The PCV7 vaccine has caused a significant decline in the incidence of pneumococcal meningitis, particularly in children younger than 2 years. Despite this overall decline, there is a notable increase in rates of non–PCV7-serotype meningitis. One of the more aggressive such serotypes, 19A, has been included in the new 13-valent pneumococcal vaccine.

Emergent diagnosis of bacterial meningitis in the post-PCV7 era continues to rely on the history, physical examination, and laboratory evaluation of CSF and peripheral blood. No single test is completely diagnostic, particularly in the pretreated patient. Most children with CSF pleocytosis do not have bacterial meningitis. The BMS can be used to identify select patients with CSF pleocytosis at very low risk for bacterial meningitis. Enteroviral PCR is also a useful diagnostic tool. Procalcitonin shows promise as a marker for bacterial infection, but further investigation is required before incorporating it into routine decision making.

Empiric antibiotic therapy in the neonate should include ampicillin with either cefotaxime or an aminoglycoside. Acyclovir should also be considered. Outside the neonatal period, vancomycin plus a third-generation cephalosporin should be used. Children with predisposing factors should receive tailored antibiotic regimens. While a sizeable percentage of pneumococcal isolates display antibiotic nonsusceptibility, there has been a marked decline in the incidence of resistant meningitis, mirroring the decline in disease overall. The role of corticosteroids is unclear. The American Academy of Pediatrics suggests that dexamethasone therapy may be useful in children with Hib meningitis if given with or before the first dose of antibiotics, but is otherwise unlikely to provide benefit. Steroids have shown no protective role against mortality in children with bacterial meningitis. Other adjunct therapies are currently being studied.

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