Pneumococcal meningitis: antibiotics essential but insufficient

Prior to the discovery of antibiotics, bacterial meningitis was almost invariably fatal: over 95% of individuals developing bacterial meningitis died, and the few individuals surviving infection were neurologically devastated. With the advent of antibiotics, bacterial meningitis became a treatable condition, and the primary objective in the patient with bacterial meningitis became, appropriately, prompt diagnosis and initiation of antibiotic therapy.

Until the latter part of the twentieth century, bacterial meningitis was predominantly a condition of infancy and early childhood, caused in large part by *Haemophilus influenzae* type B. *Streptococcus pneumoniae*, although the most common cause of meningitis in adults, received relatively little attention in terms of its pathogenesis, mechanisms of injury, and optimal therapy. Immunization against *Haemophilus influenzae* type B brought about a profound decrease in cases of early childhood meningitis in developed countries. *Streptococcus pneumoniae* is now the most common agent of bacterial meningitis for children as well as adults (Schuchat et al., 1997).

The article by Kastenbauer et al., in this issue of *Brain*, reminds us that there is much about the pathogenesis of pneumococcal meningitis which we still do not understand and that, despite antibiotics, current therapy of *S. pneumoniae* meningitis leaves much to be desired. *S. pneumoniae* is, for the most part, highly sensitive to antibiotics, yet mortality from pneumococcal meningitis remains high (24.1%) despite antibiotic therapy, and survivors are often neurologically damaged (36.4%). As Kastenbauer et al. point out, neurological injury in *S. pneumoniae* meningitis is not only due to meningeal inflammation but also to cerebral vasculitis, cerebral edema, cerebral necrosis and hydrocephalus. Less frequently appreciated, but still significant in terms of neurological injury, is the ability of the infection to cause intracranial hemorrhage as a complication of the accompanying vasculitis and, in a few cases, to cause myelitis. Hearing loss, although thought to be primarily a complication of childhood pneumococcal meningitis, was found in 20% of Kastenbauer’s adult survivors.

Kastenbauer et al. point out that pneumococcal meningitis mainly occurs in three groups of patients: 1) adults with chronic debilitating conditions such as chronic alcoholism, malignancies, chronic immunosuppressive therapy, or poorly controlled diabetes mellitus; 2) patients with asplenia; and 3) previously healthy adults with acute infections such as otitis, sinusitis, pneumonia, or endocarditis. Their article also emphasizes the importance of pneumococcal meningitis as a systemic as well as neurological condition: death in pneumococcal meningitis may result from the central nervous system infection itself, from pneumococcal sepsis with its complications of shock and disseminated intravascular coagulation – or from a combination of both intracranial and systemic insults. Thus, treatment of the patient with pneumococcal meningitis requires meticulous attention to details of general patient care well beyond that required for treatment of the meningitis itself.

Bacterial meningitis is a complex, rapidly progressive disorder in which neurological injury is caused in part by the causative organism and in part by the host’s own inflammatory response. Meningeal *S. pneumoniae* bacteria do not readily penetrate the pia and invade the brain. However, the interaction between pneumococcus and host results in meningeal inflammation, vascular injury, disruption of the blood-brain barrier, vasogenic, interstitial and cytotoxic edema, and disruption of normal CSF flow (figure 1). At the molecular level, *S. pneumoniae* cell walls have been shown to induce cerebrovascular endothelial cells, microglia, and meningeal inflammatory cells to release cytokines, chemokines and reactive oxygen species (Scheld et al., 2002). These include tumor necrosis factor alpha, interleukins 1 and 6, platelet-activating factor, peroxynitrites, matrix metalloproteinases and urokinase plasminogen activator. Release of cytokines in response to bacterial products is also believed to play a role in the development of disseminated intravascular coagulation in the setting of pneumococcal sepsis. Other components of host response will almost certainly be found to play a role in neurological injury, as well.

Modern antibiotics rapidly sterilize CSF in pneumococcal meningitis within hours to a day of initiation (Kanegaye et al., 2001). However, many of the neurological and systemic conditions which contribute to morbidity and mortality in pneumococcal meningitis – in particular vascular injury and cerebral edema – have already been set into motion by the time antibiotics are begun and are, themselves, not directly responsive to antibiotic therapy. Acute treatment of pneumococcal meningitis with dexamethasone has been found, in both adults (de Gans et al., 2002) and children (McIntyre et al., 1997), to reduce the incidence of neurological sequelae.
However, its effect is limited, and there is clear need for new adjunctive drugs which are more effective in controlling cerebral inflammation and edema. Development of these newer therapies will require greater knowledge of the molecular and pathological events involved in pneumococcal meningitis and a better understanding as to how these events may be interrupted in the patient receiving effective antibiotic therapy. Animal models of bacterial meningitis provide a powerful tool with which to study the sequence of intracranial events involved in meningeal invasion and neurological injury (Koedel and Pfister, 1999); and recent studies of experimental bacterial meningitis suggest potential benefit from several drugs that inhibit CSF cytokines, matrix metalloproteinases and reactive oxygen species. In man, cerebral neuroimaging studies, as shown by Kastenbauer et al., have the potential to monitor the intracranial consequences of meningitis in humans at multiple points in time and could help guide therapy directed at specific aspects of the infection.

Ultimate control of pneumococcal meningitis, like elimination of *Haemophilus influenzae* as a cause of early childhood meningitis, may be brought about by widespread use of effective vaccine. Multiple serotype pneumococcal vaccines are now available for children and high risk adults, but data concerning their efficacy in preventing pneumococcal meningitis is limited, and vaccine failures have been reported in asplenic individuals (Peltola, 1999). Unfortunately, in 2003 the prognosis for patients with *S. pneumoniae* meningitis remains neither qualitatively nor quantitatively different than it was thirty years ago. While antibiotics are essential, they are insufficient and research is needed to develop better adjunctive therapies.

Fig 1 Overview of mechanisms by which pneumococcal meningitis can cause brain damage.

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References


