

## Seminar

## Bacterial meningitis in children

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**This review comprises aspects of the epidemiology, microbiology, pathophysiology, clinical manifestations, diagnosis, management, prognosis, and prevention of bacterial meningitis, with emphasis on the paediatric population. The beginning of this millennium has witnessed the virtual disappearance of *Haemophilus* invasive disease in some countries, emergence of pneumococcal strains that are resistant to multiple antibiotics, isolation of pneumococci with tolerance to vancomycin, outbreaks and clusters of meningococcal meningitis in several geographical areas, and intense research in development of effective conjugate pneumococcal and meningococcal vaccines. Bacterial meningitis has become an uncommon disease in the developed world. Unfortunately, because of limited economic resources and poor living conditions, many developing countries are still affected by the devastating consequences of this life-threatening systemic infection. Basic and clinical research is needed to discover new antimicrobial and anti-inflammatory agents to improve outcome from disease. Novel strategies are needed to distribute and implement effective vaccines worldwide to prevent bacterial meningitis.**

Meningitis is a severe acute infectious disease caused by several microorganisms, including viruses, bacteria, parasites, and fungi. Fatality rates associated with this disease can be as low as 2% in infants and children, and as high as 20–30% in neonates and adults.<sup>1</sup> Transient or permanent deafness, or other neurological sequelae, arise in up to a third of survivors.<sup>2</sup> Since their advent, antimicrobial agents have had a profound effect on the clinical course and prognosis of meningitis. However, outcomes have been only modestly improved by advanced medical intensive care technology and the availability of new, very active  $\beta$ -lactam antibiotics. Further improvements in treatment can result only from a better understanding of the pathophysiological events that occur after activation of the host's inflammatory pathways by either the bacteria or their products, and of the molecular mechanisms that take part in intravascular coagulation, shock, and the genesis of brain damage.<sup>3–7</sup>

With the introduction of effective conjugated vaccines against *Haemophilus influenzae* type b organisms, the incidence of bacterial meningitis caused by this pathogen has declined by more than 99% in countries that have adopted universal immunisation.<sup>8,9</sup> This outstanding public health achievement is muted by unavailability of this vaccine worldwide, by the rapid spread of pneumococcal strains with resistance to several commonly used antimicrobial agents, and by the continued epidemics of meningococcal disease in many areas of the developing world. The introduction of conjugated vaccines against seven of the most common and resistant strains of *Streptococcus pneumoniae* causing invasive disease in children is expected to reduce the burden of invasive pneumococcal disease, including meningitis, in countries implementing universal immunisation programmes.<sup>10</sup> However, 9-valent or 11-valent vaccines will probably be

needed to deal with differences in circulating serotypes between geographical areas.<sup>11</sup> Research is now focused on development of meningococcal vaccines with improved immunogenicity against the most prevalent serogroups worldwide, including group B strains.<sup>12–14</sup>

### Bacteriology

A wide range of bacteria cause purulent meningitis. In the neonatal period, which includes premature and term babies up to 3 months of life, group B streptococci cause most bacterial meningitis in many developed countries.<sup>15</sup> Most cases are caused by subtype III strains, and the disease usually arises after the first week of life. Coliform bacilli are the second most common meningeal pathogens in this population, especially strains of *Escherichia coli* possessing K1 antigen. In many developing countries, *E coli* and other gram-negative enteric bacilli such as species of *Klebsiella*, *Enterobacter*, and *Salmonella*, are the leading cause of meningitis in newborns.<sup>16</sup> *Listeria monocytogenes* is occasionally responsible for bacterial meningitis in this age-group, especially during zoonotic outbreaks.<sup>17,18</sup> As with group B streptococcal infections, meningeal infection caused by *L monocytogenes* usually happens after the first week of life. *Listeria* serotype IVb has been implicated in most cases. In infants and small children, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *H influenzae* type b (rare in areas with routine *Haemophilus* vaccination) are the most common meningeal pathogens. Children older than

### Search strategy

We searched MEDLINE database for articles published within the past 15 years, with the keywords meningitis, bacterial meningitis, meningitis in children, bacterial meningitis in children, neuroinfection, CNS infection, brain infection, and meningeal inflammation. We also assessed classic and well-accepted older articles. We assessed articles in the English and Spanish languages, and articles published in German, French, Asiatic, Arabic, and other journals, with abstracts in the English language. Most treatment recommendations were based on data from randomised controlled trials, but expert consensus was also used when adequate assessment studies were not available.

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5 years and adults are almost exclusively affected by *S pneumoniae* and *N meningitidis*. In immunocompromised hosts and in patients undergoing neurosurgical procedures, meningitis can be caused by various different bacteria such as *Staphylococcus* species, gram-negative enteric bacilli, or *Pseudomonas aeruginosa*.<sup>19</sup>

Encapsulated strains of *H influenzae* are classified by capsular polysaccharide types a–f; however, more than 95% of invasive diseases are caused by type b strains. With the routine use of conjugated vaccines against the type b strain in many countries, disease caused by this organism has almost disappeared,<sup>8,9,20,21</sup> without replacement by other capsular types.

Although more than 90 serotypes of pneumococci have been identified on the basis of their capsular polysaccharides, few are commonly associated with invasive disease and with meningitis. Almost all penicillin-resistant pneumococcal strains causing meningitis belong to serotypes 6, 9, 14, 18, and 23.<sup>22</sup>

Meningococci have been divided into serogroups on the basis of antigenic differences in their capsular polysaccharides (A, B, C, D, X, Y, Z, W-135, and 29-E). Groups B, C, Y, and W-135 are the predominant serogroups associated with invasive disease in the USA and in other developed countries, whereas the group A strain accounts for epidemic disease in many other countries, especially sub-Saharan Africa.<sup>23</sup> Group B strains are the most common isolates in Latin America. Meningococcal serotypes are defined on the basis of antigenic differences in the class 2 and 3 outer membrane proteins, whereas differences in the class 1 outer membrane proteins determine subtypes. More than 20 serotypes and at least ten class 1 subtypes have been identified.<sup>24</sup>

### Epidemiology

The frequency of neonatal meningitis varies greatly between different institutions and geographical areas, with rates of about two to ten cases per 10 000 livebirths.<sup>25</sup> More than two-thirds of all cases of neonatal meningitis in developed countries are caused by group B streptococci and gram-negative enteric bacilli. *L monocytogenes* is encountered occasionally, and is usually associated with maternal infection acquired from contaminated milk products. In developing countries, gram-negative enteric bacilli are the predominant organisms causing bacterial meningitis in newborns; however, group B streptococci and *L monocytogenes* have been isolated increasingly.<sup>16</sup> Infections are mostly acquired by vertical transmission, but nosocomial transmission is also important, especially in preterm infants with low birthweight who require long-term intensive care. Viridans streptococci, enterococci, staphylococci, and non-typeable *H influenzae* strains can also cause meningitis. Although nearly all newborn infants are colonised by many of the organisms with which they have contact, sepsis arises in fewer than 1% of these infants. About 25% of infants with septicaemia develop meningitis.<sup>15</sup>

*H influenzae* type b meningitis is mainly a disease of infancy. Babies in the first year of life have the highest rates; most cases are in children aged 3 months to 3 years. The disease is uncommon in infants younger than 3 months and in children older than 5 years of age. During the first few months of life, most infants are protected by passively acquired maternal antibodies. Children naturally develop immunity to *H influenzae* after the third year of life, and concentrations of polyribosylribitol phosphate antibodies reach adult values by 7 years of age. Meningococcal and pneumococcal meningitis are at their highest rates in the first year of life, and rarely arise in infants younger than 3 months of age. Unlike *H influenzae*

infections, these two organisms can cause systemic infection at any age in both children and adults.

Although poor living conditions increase the risk of meningitis, other factors, such as crowded attendance in day-care facilities, contribute to the frequency of disease. However, the increased rate in some ethnic groups (American Indian, Inuit, and black people) and some families, and the observation that siblings of patients with meningitis can have deficient antibody synthesis against *H influenzae*, indicate that genetic predisposition to infection probably exists.<sup>26</sup>

Most cases of meningitis arise sporadically; only meningococcal infections can occur in epidemic form. Meningococci are transmitted from person to person by nasopharyngeal secretions from a patient or carrier, and transmission usually requires close contact. Major epidemics have happened in South America, Finland, Mongolia, and sub-Saharan Africa. Outbreaks have been noted among military recruits in training camps during every period of national mobilisation, and in students living in dormitories at US colleges.<sup>27</sup>

The risk of acquiring a secondary case of meningococcal or *Haemophilus* disease is greatly increased after exposure to primary infection in the household.<sup>28</sup> *Haemophilus* disease is most likely to be acquired by unvaccinated infants and children younger than 4 years of age, whereas for meningococcal disease the frequency of secondary cases is increased for family members of all ages.

### Pathogenesis

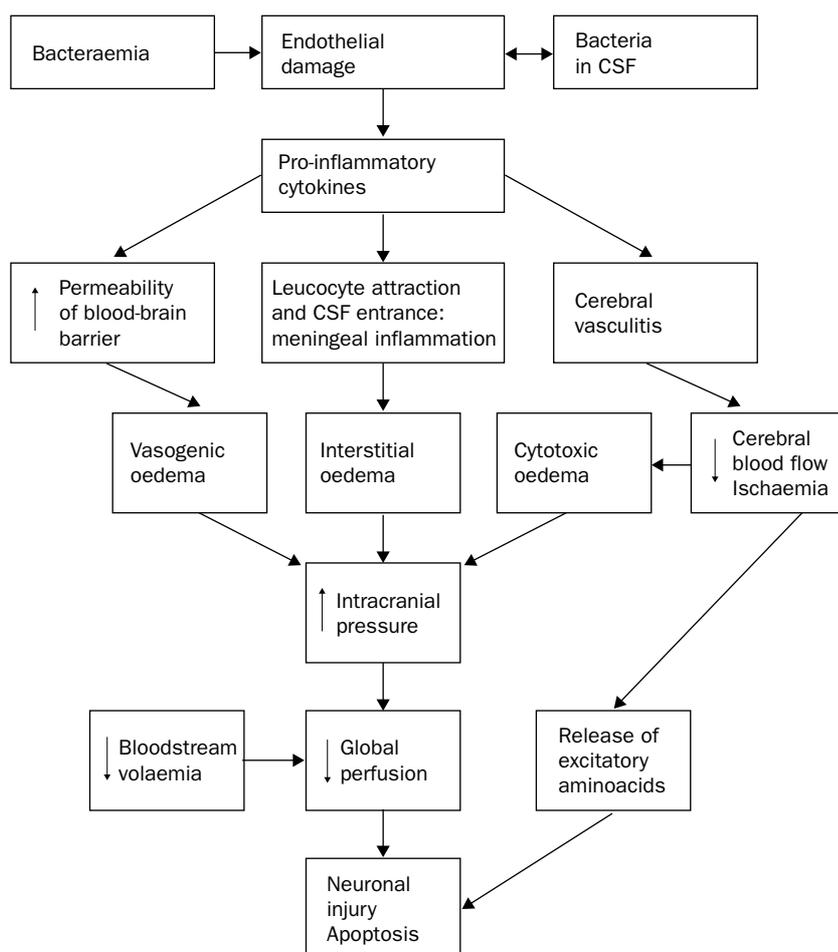
Meningitis usually follows invasion of the bloodstream by organisms that have colonised mucosal surfaces. In the neonatal period, pathogens are acquired mainly, although not exclusively, during birth by contact and aspiration of intestinal and genital tract secretions from the mother. Neonates with longer nursery stays can also be exposed to multiple nosocomial pathogens.

In infants and children, meningitis usually develops after encapsulated bacteria that have colonised the nasopharynx are disseminated in the blood. Viral infections of the upper respiratory tract commonly precede invasion of the bloodstream. Subsequently, organisms penetrate vulnerable sites of the blood-brain barrier (eg, choroid plexus and cerebral capillaries) and reach the subarachnoid space.<sup>5</sup>

Meningitis can also develop by direct extension of infection from a paranasal sinus or from the middle ear through the mastoid to the meninges. Severe head trauma with a skull fracture, cerebrospinal fluid (CSF) rhinorrhoea, or both, can lead to meningitis, usually caused by *S pneumoniae*. Bacteria can be directly inoculated into the CSF by congenital dural defects (dermal sinus or meningomyelocele), neurosurgical procedures (such as CSF diversion shunts), penetrating wounds, or extension from a suppurative parameningeal focus.

### Pathophysiology

The intense inflammation within the subarachnoid space noted in lumbar CSF, and the resulting neurological damage, are not the direct result of the pathogenic bacteria but rather of activation of the host's inflammatory pathways by the microorganisms or their products (figure).<sup>4</sup> When the pathogens have entered the central nervous system, they replicate rapidly and liberate active cell wall or membrane-associated components—ie, lipoteichoic acid and peptidoglycan fragments of gram-positive organisms, and lipopolysaccharide of gram-negative bacteria. Antibiotics that act on cell walls cause rapid lysis of bacteria, which can initially cause enhanced release of these active bacterial products into the CSF.<sup>29,30</sup> These potent inflammatory



#### Pathophysiological cascade in bacterial meningitis

substances can stimulate macrophage-equivalent brain cells (eg, astrocytes and microglia), cerebral capillary endothelia, or both, to produce cytokines such as tumour necrosis factor, interleukin-1, and other inflammatory mediators such as interleukin-6, interleukin-8, platelet-activating factor, nitric oxide, arachidonic acid metabolites (eg, prostaglandin and prostacycline), and macrophage-derived proteins.<sup>4,31,32</sup> The cytokines activate adhesion-promoting receptors on cerebral vascular endothelial cells and leucocytes, attracting neutrophils to these sites.

Subsequently, leucocytes penetrate the intercellular junctions of the capillary endothelium and release proteolytic products and toxic oxygen radicals. These events result in injury to the vascular endothelium and alteration of blood-brain barrier permeability. Dependent on the potency and duration of the inflammatory stimuli, the alterations in permeability allow penetration of serum proteins of low molecular-weight into the CSF, and lead to vasogenic oedema. Additionally, large numbers of leucocytes enter the subarachnoid space and release toxic substances that contribute to the production of cytotoxic oedema. As a result of the high protein and cell content, the increased viscosity of the CSF contributes to generation of interstitial oedema. All these inflammatory events, if they are not modulated promptly and effectively, eventually cause alteration of CSF dynamics (brain oedema, intracranial hypertension), of brain metabolism, and of cerebrovascular autoregulation (reduced cerebral blood flow).<sup>33-35</sup> Research is now focused on delineation of the mechanisms with a role in neuronal injury, possibly through the participation of potential mediators such as reactive oxygen and nitrogen

substances, excitatory aminoacids, metalloproteinases, and caspases that mediate cellular apoptosis.<sup>3,6,35,36</sup> Additionally, much evidence suggests that a complex network of cytokines, chemokines, proteolytic enzymes, and oxidants take part in the inflammatory cascade that leads to tissue destruction in bacterial meningitis. Genetic targeting or pharmacological blockade of these molecular pathways, or both, might prevent the irreversible focal or diffuse brain damage frequently associated with disease.<sup>37</sup>

#### Clinical manifestations

The clinical picture of acute bacterial meningitis mainly depends on the patient's age. The classic manifestations noted in older children and adults are rarely present in infants. In general, the younger the patient, the more subtle and atypical are the signs and symptoms. Classic meningitis of children and adults usually begins with fever, chills, vomiting, photophobia, and severe headache. Occasionally, the first sign of illness is a convulsion that can recur during progression of the disease. Irritability, delirium, drowsiness, lethargy, and coma can also develop. As the CSF inflammatory response intensifies in bacterial meningitis, the most consistent physical finding, in children and adults, is the presence of nuchal rigidity associated with Brudzinski's and Kernig's signs.

These signs and symptoms are common to all types of meningitis.<sup>38</sup> Other manifestations, however, are associated with specific infections. Petechial and purpuric eruptions are usually indicative of meningococcaemia, although they can be present in *H influenzae* meningitis. Rashes very rarely occur with pneumococcal infections. The rapid development of multiple haemorrhagic eruptions in association with a shocklike state is almost pathognomonic of meningococcaemia (Waterhouse-Friderichsen syndrome). Implication of the joints suggests infection with meningococci or *H influenzae*, and can arise early (suppurative arthritis) or late (reactive arthritis) in the illness. The presence of a chronically draining ear or a history of head trauma with or without skull fracture is most likely to be associated with pneumococcal meningitis.

#### Diagnosis

A definitive diagnosis of meningitis is dependent on examination and culture of CSF. Whenever the physician suspects meningitis, a lumbar puncture should be undertaken. Early diagnosis followed by appropriate medical management can have a favourable effect on outcome. In neonates, the procedure should be considered when sepsis is suspected, because meningitis accompanies sepsis in 20–25% of cases. In infants, fever and convulsions may be the only initial signs of meningitis.

When focal neurological signs, especially pupillary signs or cardiovascular instability, are present, whether accompanied by papilloedema or not, the use of cranial CT or magnetic resonance imaging should be considered before the lumbar puncture, to exclude a brain abscess or

generalised cerebral oedema, and to avoid the danger of herniation.

Examination of the CSF of a patient with acute bacterial meningitis characteristically reveals a cloudy fluid, consisting of an increased white blood cell count and predominance of polymorphonuclear leucocytes, a low glucose concentration in relation to serum value, a raised concentration of protein, and a positive stained smear and culture for the causative microorganism.<sup>25,39,40</sup>

In rare instances, especially very early in the illness, the cell count can be normal despite a positive CSF culture. In these cases, a lumbar puncture repeated several hours later usually shows raised leucocyte values. A glucose concentration of less than 200 mg/L in CSF is associated with a higher rate of hearing impairment.

The probability of visualising bacteria on a gram-stained preparation of CSF is dependent on the number of organisms present. The lower limit of detection is about  $10^5$  colony-forming units/mL in CSF, which equates to a positive stained smear in 70–80% of cases.<sup>41</sup> The sensitivity is low, however, when *L. monocytogenes* is the cause of meningitis, because usually a small number of organisms ( $\leq 10^3$  colony-forming units/mL) is present in CSF. The presence of many bacteria in every field on a stained smear shows more than  $10^7$  colony-forming units/mL, and is associated with poor prognosis. The yield of positive CSF cultures falls from 70–85% to below 50% in patients previously treated with antibiotics (especially in meningococcal infection), although change in the CSF inflammatory indices is often insignificant.

A promising diagnostic device has been developed, in which a broad range of bacterial primers for DNA amplification is used to rapidly detect conserved regions of the microbial 16S RNA gene in the CSF. Preliminary results have been associated with high sensitivity, specificity, and predictive values to diagnose bacterial meningitis. If these findings are confirmed and techniques are commercially implemented, many of the pre-treated, culture-negative cases could be identified.<sup>42-44</sup>

In patients who have received effective antimicrobial treatment before the first lumbar puncture, the CSF findings will probably be modified, but are usually still indicative of bacterial meningitis.<sup>45</sup> On the second day of treatment, the leucocyte count can be higher than at the time of diagnosis. Thereafter the count decreases, and lymphocytes can be predominant by the fifth day or later. Gram-stained smear and culture may be negative in pretreated patients. Concentrations of glucose and protein in CSF will generally remain abnormal for several days despite effective treatment.

### Complications

Complications of acute bacterial meningitis can develop early in the course of illness, either before diagnosis or several days after starting treatment. Systemic circulatory problems usually arise during the first day in hospital with acute bacterial meningitis. Peripheral circulatory collapse is one of the most striking and serious complications of meningitis. It is most frequently associated with meningococcaemia, but can accompany other types of infection.<sup>38</sup> Profound shock usually develops early in the course of the illness and, if untreated, progresses rapidly to a fatal outcome. Disseminated intravascular coagulation can be an associated finding. Gangrene of the distal extremities can occur in patients with fulminant haemorrhagic meningococcal meningitis. In some patients, treatment with antibiotics can initially aggravate these systemic problems, probably as a result of release of active

components such as endotoxin from the cell walls or membranes of rapidly lysed microorganisms.<sup>4</sup>

In the past, many patients with bacterial meningitis were believed to have inappropriate secretion of antidiuretic hormone, a condition which would require fluid restriction in the initial management of patients with neuroinfection. However, results of experimental and clinical investigations in the past decade have suggested that the raised concentration of antidiuretic hormone in serum is an appropriate host response to unrecognised hypovolaemia, and that liberal use of parenteral fluids can be beneficial.<sup>46-49</sup> This knowledge is important, because systemic blood pressure should be maintained at levels sufficient to prevent compromise of cerebral perfusion.

Focal neurological findings such as hemiparesis, quadriparesis, facial palsy, and visual field defects arise early or late in about 10–15% of patients with meningitis, and can correlate with persistent neurological abnormalities in long-term follow-up assessments.<sup>38,50</sup> Presence of focal signs can be associated with cortical necrosis, occlusive vasculitis, or thrombosis of the cortical veins. Extension of the meningeal inflammatory process can implicate the second, third, sixth, seventh, and eighth cranial nerves that course through the subarachnoid space. Inflammation of the cochlear aqueduct and the auditory nerve can lead to reversible or permanent deafness in 5–30% of patients.<sup>51</sup> Hydrocephalus, of either the communicating or obstructive type, is occasionally seen in patients in whom treatment has been either suboptimal or delayed, arising more often in younger infants. Rarely, brain abscesses can complicate the course of meningitis, especially in newborn infants infected with *Citrobacter diversus* or *Proteus* species.<sup>52</sup>

Seizures occur before, or during the first several days after, admission to hospital in as many as one-third of patients with meningitis. Although most of these episodes are generalised, focal seizures are more likely than generalised ones to presage an adverse neurological outcome. Additionally, seizures that are difficult to control or that persist beyond the fourth day in hospital, and seizures that arise for the first time late in the patient's hospital course have a greater likelihood of being associated with neurological sequelae.<sup>38</sup>

Subdural effusions are not generally associated with signs and symptoms, commonly resolve spontaneously, are present in more than one-third of patients with meningitis, and usually are not associated with permanent neurological abnormalities.<sup>53</sup> These collections are less frequently present with meningococcal than with *H. influenzae* or pneumococcal meningitis. Subdural effusions arise mainly in infants younger than 2 years of age. Indications for needle puncture of a subdural effusion include a clinical suspicion that empyema is present (prolonged fever and irritability, stiff neck coupled with CSF leukocytosis), a rapidly enlarging head circumference in a child without hydrocephalus, focal neurological findings, and evidence of increased intracranial pressure.

Joints can be affected initially or during the course of bacterial meningitis. Early occurrence suggests direct invasion of the joint by the microorganism, usually *H. influenzae* type b, whereas arthritis that develops after the fourth day of treatment is thought to be an immune-complex-mediated event that affects several joints and is most frequently seen with meningococcal infections.<sup>38</sup>

### Prognosis

The outlook in individual patients with bacterial meningitis is correlated with many factors, including age of patient, time and clinical stability before effective

## Panel 1: Penetration and estimated bactericidal power of antibiotics used for treatment of bacterial meningitis

Antibiotic	CSF penetration	Bactericidal power* against		pK/pD index†
		β-lactam susceptible pathogens	β-lactam resistant pathogens	
Penicillin/ampicillin	5–15%	1–10	<1	T/MBC
Chloramphenicol	>20%	>10	n/a‡	AUC/MBC
Cefotaxime/ceftriaxone	5–15%	>10	1–10	T/MBC
Cefepime/meropenem	5–15%	>10	1–10	T/MBC
Vancomycin	<5%	1–10	1–10	AUC or PEAK/MBC
Fluoroquinolones	>20%	>10	>10	AUC or PEAK/MBC

n/a=not applicable). T=time. AUC=area under the curve. MBC=minimal bactericidal concentration. \*Concentration in CSF over the minimal bactericidal concentration against the isolated pathogen. †Best pharmacokinetic/pharmacodynamic variable to predict bactericidal effectiveness efficacy in CSF.<sup>66–69</sup> ‡A bacteriostatic antibiotic against non-susceptible organisms. T/MBC=duration of time that CSF antibiotic concentrations exceed MBC. AUC/MBC=area under the curve over MBC. PEAK=maximal CSF antibiotic concentration.

antibiotic treatment is begun, type of microorganism, number of bacteria or quantity of active bacterial products in CSF at the time of diagnosis, intensity of the host's inflammatory response, and time elapsed to sterilise CSF cultures.<sup>4,32,54,55</sup>

As a rule, patients at the extremes of age have the poorest outlook. The highest rates of mortality and morbidity occur in the neonatal period and in the elderly. Infections caused by group B streptococci, gram-negative enteric bacilli, and pneumococci are associated with poorer outcome from disease than those caused by *H influenzae* and meningococci. In some patients, delay in initiation of antimicrobial treatment or sterilisation of CSF cultures can raise the rate of adverse outcome. The amount of bacteria or their products correlates with an increased host production of inflammatory mediators such as tumour necrosis factor, interleukin-1, and prostaglandins. The greater the host's inflammatory response in the subarachnoid space to the microorganism and its products, the greater is the likelihood of permanent sequelae.

With prompt and adequate antimicrobial and supportive treatment, the chances for survival today are excellent, especially in infants and children, for whom case fatality rates have been reduced to less than 10% and for meningococcal meningitis less than 5%. Rates of long-term sequelae, however, have not been greatly reduced, despite advances in treatment. The rate of residual abnormalities in children and adults after meningitis is about 15% (range of

10% to >30%).<sup>38</sup> Infants and children who survive bacterial meningitis are more likely to have seizures, hearing deficits, learning and behavioural problems, and lower intelligence compared with their healthy siblings who have not had meningitis. During the past decade, findings of several studies have shown that residual neurological and hearing abnormalities can be reduced in patients who received early treatment with dexamethasone.<sup>56–64</sup>

### Treatment Antimicrobials

Choice of antibiotic treatment entails the selection of agents that are effective against the probable pathogens and are able to attain adequate bactericidal activity in CSF.<sup>19,65,66</sup> The estimated bactericidal power of various antimicrobial drugs in CSF cultures has been extrapolated to man from calculation of different pharmacokinetic and pharmacodynamic variables (panel 1). The initial empiric regimen chosen for treatment should be broad enough to cover the potential organisms for the age group affected (panel 2). When the specific pathogen is identified and results of susceptibilities are known, treatment can be modified accordingly (panel 3).

In neonates, the initial empiric regimen used conventionally has been ampicillin and an aminoglycoside. Because of the emergence of aminoglycoside-resistant gram-negative enteric bacilli in some neonatal units, the concern about possible adverse auditory and renal effects,

## Panel 2: Recommended initial empiric selection of antibiotics for previously healthy children with suspected bacterial meningitis, by age and epidemiological situation

Patients	Likely pathogens	Antibiotic
Neonate		
Early-onset acquisition	<i>S agalactiae</i> , <i>E. coli</i> , <i>K pneumoniae</i> , enterococci, <i>L monocytogenes</i>	Ampicillin+cefotaxime
Late-onset infection	<i>S aureus</i> ,* gram-negative enteric bacilli, <i>P aeruginosa</i>	Nafcillin (flucloxacillin) or Vancomycin+ceftazidime†
Age: 1–3 months	Same as early-onset in neonate + <i>S pneumoniae</i> , <i>N meningitidis</i> , and <i>H influenzae</i>	Ampicillin+cefotaxime or ceftriaxone
Age: 3 months to 5 years	<i>S pneumoniae</i> , <i>N meningitidis</i> , and <i>H influenzae</i> ‡	Cefotaxime or ceftriaxone
Age: >5 years children and adults in areas with moderate or greater prevalence of resistant <i>S pneumoniae</i>	<i>S pneumoniae</i> and <i>N meningitidis</i> Multi-resistant pneumococci	Cefotaxime or ceftriaxone Cefotaxime or ceftriaxone +vancomycin (consider addition of rifampicin§)

\*Methicillin-susceptible or resistant strains. †With or without the addition of an aminoglycoside. ‡This pathogen is almost disappearing in children fully immunised with Hib vaccine. §For cephalosporin-resistant pneumococcal isolates.

## Panel 3: Suggested pathogen-specific antimicrobial therapy for children with bacterial meningitis

Bacteria	Antibiotic of choice	Other useful antibiotics
<i>N meningitidis</i> *	Penicillin G or ampicillin	Cefotaxime or ceftriaxone
<i>H influenzae</i>	Cefotaxime or ceftriaxone	Ampicillin, chloramphenicol†
<i>S pneumoniae</i> :		
Penicillin-susceptible (MIC<0.1 mcg/mL)	Penicillin G, ampicillin	Cefotaxime or ceftriaxone
Penicillin-intermediate (MIC=0.1–1.0 mcg/mL)	Cefotaxime or ceftriaxone plus vancomycin when MIC >0.5 mcg/mL	Cefepime or meropenem
Penicillin-resistant (MIC>1.0 mcg/mL)	Cefotaxime or ceftriaxone plus vancomycin‡	Cefepime or meropenem <sup>70,71</sup> plus vancomycin†
Cephalosporin-resistant (MIC>0.5 mcg/mL)	Cefotaxime or ceftriaxone plus vancomycin	Adding rifampicin <sup>72</sup> New fluoroquinolones?
<i>L monocytogenes</i>	Ampicillin+gentamicin	Trimethoprim-sulfamethoxazole
<i>S agalactiae</i>	Penicillin G+gentamicin	Ampicillin+gentamicin
Enterococcus species	Ampicillin+aminoglycoside	Vancomycin+aminoglycoside
Enterobacteriaceae	Cefotaxime or ceftriaxone	Cefepime or meropenem
<i>P aeruginosa</i>	Ceftazidime+aminoglycoside	Cefepime or meropenem

MIC=minimum inhibiting concentration. \*A third-generation cephalosporin is advised for strains with diminished penicillin susceptibility. †In areas with economic constraints. Up to 50% of *H influenzae* isolates can be resistant. ‡Vancomycin is administered until results of cefotaxime susceptibility is known. §Activity of cefepime and meropenem for penicillin-resistant *S pneumoniae* is uncertain.

and the low bactericidal activity of aminoglycosides in CSF, many centres in the USA and other countries now use ampicillin and cefotaxime instead. Although cefotaxime is effective for treatment of bacterial meningitis, concerns have arisen that the routine use of a cephalosporin in neonatal intensive care units will lead to rapid emergence of resistant organisms, especially among gram-negative bacilli. However, the use of cefotaxime also has advantages; the drug has high bactericidal activity in CSF against most coliforms, and, unlike aminoglycoside, concentrations in serum do not need to be monitored to attain safe and therapeutic values. Ceftriaxone, although equivalent in activity to cefotaxime, is not recommended for use in the neonatal period because of the potential displacement of bilirubin from albumin-binding sites and its profound inhibitory effect on growth of bacterial flora of the intestinal tract.<sup>73</sup>

In newborns with meningitis caused by susceptible gram-negative enteric organisms, cefotaxime can be used safely and effectively, either alone or combined with an aminoglycoside. For meningitis caused by group B streptococci or *L monocytogenes*, ampicillin alone is usually satisfactory after an initial 48–72 h of combined therapy with an aminoglycoside. For disease caused by a rare tolerant strain of group B *Streptococcus* (ie, one which is inhibited but not killed by achievable CSF concentrations of ampicillin) or by an *Enterococcus* species, combination therapy with ampicillin and an aminoglycoside is indicated.<sup>15</sup>

The duration of treatment for neonatal meningitis depends on the clinical response and duration of positive CSF cultures after treatment is started. Ten to 14 days is usually satisfactory for disease caused by group B *Streptococcus* and *L monocytogenes*, and a minimum of 3 weeks of treatment is needed for gram-negative enteric meningitis. *Enterococcus* meningitis is usually treated for 2–3 weeks. Because of the unpredictable clinical course of illness and the unreliability of the clinical examination in assessment of response to treatment in neonates, we believe that the CSF should be examined and cultured at completion of treatment to establish whether additional treatment is required. Additionally, we recommend that a cranial CT scan or MRI should be undertaken during treatment to ascertain that intracranial complications have not occurred.

In infants aged 1–3 months, ampicillin and ceftriaxone or cefotaxime constitute a suitable initial empiric regimen, because in some patients *Listeria* or enterococci (which are resistant to the cephalosporin) can be the causative agent. Addition of vancomycin to the third-generation cephalosporin is advised when *S pneumoniae* is suspected on the basis of a CSF smear in areas where pneumococcal strains with resistance to penicillin and cephalosporin have been noted.

Monotherapy with cefotaxime or ceftriaxone is usually a part of management for infants, children, and most adults, because of the extraordinary in-vitro activity of these drugs against the common meningeal pathogens, their excellent safety record, and their ability to promptly sterilise CSF cultures.<sup>15,25,74,75</sup> Chloramphenicol is rarely used at present in developed countries, because of its unpredictable metabolism in young infants, its pharmacological interaction when administered concomitantly with phenobarbital, phenytoin, rifampin, or acetaminophen, and the need to monitor its concentration in serum to avoid toxic or subtherapeutic values. For economic reasons, however, chloramphenicol is frequently used as initial empiric therapy for meningitis in developing countries. The effectiveness of this antibiotic has fallen as *Haemophilus* strains have become resistant to chloramphenicol, and multidrug-resistant pneumococci are usually not killed by this agent. For meningococcal meningitis, a short course of chloramphenicol treatment is commonly used in African countries with reasonable success.<sup>76</sup>

Another reason for use of third-generation cephalosporins in the management of meningitis is that 20–45% of *S pneumoniae* strains, worldwide, are resistant to penicillin.<sup>77–80</sup> As many as two-thirds of these strains have intermediate resistance (minimum inhibitory concentration 0.1–1.0 g/L), and the rest are deemed highly resistant (>1.0 g/L). These strains can be also resistant to chloramphenicol and to third-generation cephalosporins. Although many of the infections caused by strains with intermediate resistance can be successfully treated with either cefotaxime or ceftriaxone, we recommend the addition of vancomycin to the initial empiric regimen to ensure eradication of these strains from CSF. Worryingly, pneumococcal strains exhibiting vancomycin tolerance have been isolated in vitro and in vivo; the clinical significance of this finding is uncertain.<sup>81,82</sup> To avoid potential failure of antimicrobials in

patients infected by multi-resistant or tolerant meningeal pathogens in the near future, new antimicrobials such as fluoroquinolones (eg, gatifloxacin, moxifloxacin, and garenoxacin) are currently undergoing both preclinical and clinical assessment.<sup>83</sup> Trovafloxacin—a quinolone drug that is no longer marketed in many countries—has been shown to have similar efficacy to ceftriaxone with or without vancomycin in children with meningitis, including those infected with  $\beta$ -lactam resistant pneumococci.<sup>84</sup> Strains of *N meningitidis* with part resistance to penicillin have also been encountered in the USA and some other parts of the world.<sup>85,86</sup> Although no clinical failures of penicillin treatment have yet been reported in patients with meningitis caused by these isolates, the initial cephalosporin monotherapy should be continued for 4–5 days, when economically feasible.

We strongly recommend that a repeat lumbar puncture should be done at 24–48 h after admission if a resistant pneumococcus has been isolated from the initial CSF culture, and if the patient has not shown clear clinical improvement. Modification of the antimicrobial regimen should be made according to bacteriological and clinical findings. 4–7 days of treatment is satisfactory for most infants and children with uncomplicated meningococcal meningitis, 7–10 days for *Haemophilus* disease, and 10 days or longer for pneumococcal meningitis.

#### Supportive and adjunctive treatment

Adequate oxygenation, prevention of hypoglycaemia and hyponatraemia, anticonvulsant treatment, and measures designed to decrease intracranial hypertension and to prevent fluctuation in cerebral blood flow are crucial in the management of patients with bacterial meningitis (panel 4).<sup>87</sup>

Optimum cerebral perfusion can be maintained by controlling fever to reduce the brain's metabolic demands, by maintaining arterial blood pressures within normal limits, and by hyperventilation to reduce arterial carbon dioxide tension to a range of 25–30 mm Hg. However, some authorities believe that hyperventilation should not be used in children with bacterial meningitis and evidence of cerebral oedema on CT scan, because intracranial pressure would be decreased at the expense of a reduction in cerebral blood flow, possibly approaching ischaemic thresholds.<sup>88</sup>

Several double-blind, placebo-controlled studies have been undertaken to assess the role of steroids in infants and children with bacterial meningitis.<sup>56–63</sup> In most trials, treatment with dexamethasone was associated with improvement in meningeal inflammatory indices, with

reduction in CSF cytokine concentrations, and with fewer audiological and neurological sequelae compared with placebo recipients, especially in children with *Haemophilus* meningitis. Superior outcome compared with placebo recipients was noted when dexamethasone was given early (ie, before the first parenteral dose of antibiotic) as opposed to late (ie, after several hours or more of starting antimicrobial treatment).<sup>62</sup> Findings in animals have confirmed the importance of timing to achieve the most beneficial effects with dexamethasone treatment. Initially, investigators used a dexamethasone dosage of 0.15 mg/kg every 6 h for 4 days. Further evidence suggests that similar beneficial results can be obtained by using a dosage of 0.4 mg/kg every 12 h for 2 days.<sup>62,89</sup>

Although most of the cases of meningitis in these prospective studies were caused by *H influenzae*, data suggest that the salutary effects associated with dexamethasone treatment also apply to pneumococcal meningitis. Concern, however, has been raised with the use of steroids in patients with infection caused by highly-resistant pneumococcal strains, because of the decreased penetration of antibiotics when dexamethasone is used.<sup>38,72,90</sup> To date, available clinical data suggest that dexamethasone does not interfere with the eradication of resistant pneumococci by combined treatment with a third-generation cephalosporin and vancomycin. In view of these data, we believe that the advantages of dexamethasone treatment, when given before the first parenteral dose of antibiotic, outweigh the possible disadvantages, and we continue to recommend this drug for management of bacterial meningitis in infants and children. Some physicians, however, do not recommend adjunctive steroid treatment, especially now that *H influenzae* meningitis has disappeared in the USA and in other developed countries and many pneumococcal strains are currently resistant to  $\beta$ -lactam antibiotics. The emerging data on pneumococcal isolates with vancomycin tolerance, and the putative role of dexamethasone in aggravating neuronal apoptosis of the hippocampus in animal models of meningitis, suggest the need for caution in the future.<sup>91,92</sup>

An absence of beneficial effects with dexamethasone has been shown in malnourished African children with bacterial meningitis.<sup>93</sup> Interpretation and application of these results is difficult, especially in developed countries, since the findings might have been affected by use of suboptimal antibiotic treatment (presumably associated with delayed bacterial CSF clearance and poor cell-wall lytic activity), delayed access to medical attention and treatment, immunosuppression by HIV, and high early rates of

#### Panel 4: Commonly-used supportive and adjunctive treatment in bacterial meningitis

Rationale	Strategies	Cautions
Reduction of raised intracranial pressure	30° bed head elevation, antipyretic agents, avoidance of vigorous and frequent intratracheal suctioning and intubation, correction of hyponatraemia and SIADH, hyperventilation, use of mannitol, high-dose barbiturate therapy	Fluid restriction can be dangerous if patient has dehydration or hypovolaemia; significant reduction of PaCO <sub>2</sub> (<25 mm Hg) can affect cerebral blood flow; cardiac toxicity with pentobarbital
Control and prevention of seizures	Anticonvulsant drugs (lorazepam, diazepam, phenytoin, phenobarbital)	Respiratory depression and hypotension with benzodiazepines and phenobarbital; cardiac arrhythmias with phenytoin
Amelioration of meningeal inflammation	Dexamethasone	Potential delayed eradication of highly-resistant pneumococci from CSF; rare risk of GI bleeding; possibly, long-term cognitive impairment due to cell apoptosis in hippocampus

CSF=cerebrospinal fluid. SIADH=syndrome of inappropriate secretion of anti-diuretic hormone. GI=gastrointestinal.

morbidity and fatality.<sup>94</sup> In another large clinical trial in adults with bacterial meningitis, with excellent methodological design and early administration of steroids, treatment with dexamethasone was associated with a reduction in mortality and a more favourable outcome (74% *vs* 48% for dexamethasone and placebo, respectively), even in patients infected with *S pneumoniae*.<sup>95</sup>

When severe manifestations of sepsis accompany meningitis, notably in meningococcaemia, other adjunctive drugs might be effective. Recent data suggest that treatment with recombinant bactericidal permeability-increasing protein could potentially be useful in children with meningococcal systemic infection.<sup>96,97</sup> Treatment of severe sepsis in adults with human recombinant protein C improves outcome from disease by ameliorating the activation of the coagulation and inflammatory cascade.<sup>98</sup> Although these two agents could reduce the severity of sepsis, they are not expected to interfere with the meningeal inflammatory alterations because their penetration into CSF is likely to be poor.

### Prevention Vaccination

Immunisation is the most effective means of prevention of bacterial meningitis in children. Before vaccination, 60–70% of all *H influenzae* meningitis cases were in infants younger than 18 months old. The new conjugated *Haemophilus* vaccines are much more immunogenic than the polysaccharide vaccine, and findings of studies in Finland and in the USA show excellent immunogenicity and protection after initiation of a four-dose (three primary and one booster dose) vaccine regimen at 2–3 months of age.<sup>99,100</sup> Universal immunisation with these conjugated vaccines has been associated with a reduction of more than 99% in invasive diseases caused by *H influenzae* type b in developed countries.<sup>9</sup> The costs and implementation of these vaccines in developing countries pose daunting problems that can only be overcome by collaborative efforts of the vaccine manufacturers, WHO, and philanthropic foundations.

A polyvalent meningococcal vaccine, containing the purified polysaccharide capsules of group A, C, Y, and W-135 organisms, is available, but it is not recommended for general use in infants and young children because of inconsistent immunogenicity at young ages.<sup>24</sup> The vaccine has been recommended for children older than 2 years who are at high risk of infection, such as those with asplenia and with terminal complement deficiencies, and students living in dormitories. The emergence of serogroup W-135 in Africa merits an international effort to introduce this quadrivalent vaccine to potentially prevent millions of cases of meningococcal disease.<sup>101</sup> Several European countries have recently adopted routine vaccination against group C meningococcal disease with a new conjugated vaccine.<sup>102,103</sup> Preliminary information obtained in Great Britain suggests that universal vaccination against group C meningococcus reduced disease prevalence.<sup>103,104</sup> Cuba and Norway have also manufactured outer membrane proteins vaccines against the group B meningococcus. Field trials in several parts of the world showed a modest estimated efficacy of this vaccine; the lowest protection was recorded in young children.<sup>12,24</sup> Vaccines for multiple meningococcal serotypes need to be more immunogenic to prevent these infections in infants and young children. Ongoing experimental and clinical research of meningococcal vaccine candidates is encouraging.

In 2000, a new conjugate vaccine, directed against the seven most prevalent pneumococcal strains causing invasive disease in the USA, was approved for routine use

in infants, starting at 2 months of age.<sup>105,106</sup> Three doses of this vaccine, given at 2, 4, and 6 months of age, were associated with a reduction of more than 90% in invasive pneumococcal infections, including sepsis and meningitis.<sup>10</sup> Thus, an important decline of pneumococcal meningitis cases is expected to arise in the near future in countries that implement universal immunisation in infancy. As a result, inclusion of vancomycin in the initial, empiric regimen might no longer be necessary, because the prevalence of  $\beta$ -lactam resistant pneumococci would be greatly reduced.

### Chemoprophylaxis

Intrapartum ampicillin or penicillin given to women at high risk (with prenatal vaginal or rectal colonisation with group B streptococcal) has been associated with reduced rates of neonatal colonisation and of early-onset group B streptococcal sepsis.<sup>107,108</sup> However, most cases of group B streptococcal meningitis present later in the neonatal period, intrapartum prophylaxis has not substantially reduced the frequency of these late-onset cases. Conjugated group B streptococcal vaccines are immunogenic in women of child-bearing years, and could be effective in prevention of most infections in newborn infants.<sup>109</sup>

In infants and children, rifampin prophylaxis for *Haemophilus* disease is recommended for all household contacts, irrespective of age, when at least one unvaccinated contact is younger than 4 years of age.<sup>28</sup> Household and day-care contacts of a person with an index case of meningococcal disease should be also given rifampin prophylaxis. Ceftriaxone given in a single intramuscular dose (125 mg for children younger than 12 years; 250 mg for those older than 12 years and adults) is more effective than oral rifampin in elimination of meningococcal group A nasopharyngeal carriage; therefore it can be used when oral rifampin cannot be taken (eg, during pregnancy) or when compliance with the oral regimen is unlikely.<sup>110</sup> One oral dose of ciprofloxacin, ofloxacin, or azithromycin can also eradicate meningococcal carriage in adults.<sup>111</sup>

### Future challenges

In the past decade, two major advances were accomplished in the field of bacterial meningitis: an improved understanding of the basic mechanisms of disease, and the virtual elimination of *Haemophilus* meningitis as a result of universal vaccination programmes. Nevertheless, important challenges remain to be solved. We need to assess new antimicrobial agents that are effective against resistant and tolerant pneumococcal strains. More importantly, new candidate vaccines against the most important bacterial types of *S pneumoniae*, *N meningitidis*, and *S agalactiae* causing meningitis will need to be assessed in developed and developing countries. A universal effort must be put in action to make effective vaccines available for the underserved population of the world. Finally, the deciphering of the human genome, and its potential clinical implications, make plausible the assumption that in the future new genetic methods will be available to predict our vulnerability to specific meningeal pathogens, response to antimicrobial agents and vaccines, and outcome from disease.

#### Conflict of interest statement

X Sáez-Llorens and G H McCracken Jr will be taking part in a study of gatifloxacin in meningitis, sponsored by Bristol-Myers Squibb.

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