Acute bacterial meningitis in infants and children

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Bacterial meningitis continues to be an important cause of mortality and morbidity in neonates and children throughout the world. The introduction of the protein conjugate vaccines against *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis* has changed the epidemiology of bacterial meningitis. Suspected bacterial meningitis is a medical emergency and needs empirical antimicrobial treatment without delay, but recognition of pathogens with increasing resistance to antimicrobial drugs is an important factor in the selection of empirical antimicrobial regimens. At present, strategies to prevent and treat bacterial meningitis are compromised by incomplete understanding of the pathogenesis. Further research on meningitis pathogenesis is thus needed. This Review summarises information on the epidemiology, pathogenesis, new diagnostic methods, empirical antimicrobial regimens, and adjunctive treatment of acute bacterial meningitis in infants and children.

Introduction

Bacterial meningitis, an inflammation of the meninges affecting the pia, arachnoid, and subarachnoid space that happens in response to bacteria and bacterial products, continues to be an important cause of mortality and morbidity in neonates and children.[1–4] However, mortality and morbidity vary by age and geographical location of the patient and the causative organism. Patients at risk for high mortality and morbidity include newborns, those living in low-income countries, and those infected with Gram-negative bacilli and *Streptococcus pneumoniae*.[1–4] Severity of illness on presentation (eg, low score on Glasgow coma scale), infection with antimicrobial-resistant organisms, and incomplete knowledge of the pathogenesis of meningitis are additional factors contributing to mortality and morbidity associated with bacterial meningitis.[1–7]

Suspected bacterial meningitis is a medical emergency; thus, immediate steps must be taken to establish the specific diagnosis, and empirical antimicrobial treatment must be started rapidly. The mortality of untreated bacterial meningitis approaches 100% and, even with optimum treatment, mortality and morbidity might happen. Neurological sequelae are relatively common in survivors of meningitis, particularly after pneumococcal meningitis.[1–6]

Epidemiology

Almost all microbes that are pathogenic to human beings have the potential to cause meningitis, but a relatively small number of pathogens (ie, group B streptococcus, *Escherichia coli*, *Listeria monocytogenes*, *Haemophilus influenzae* type b [Hib], *S pneumoniae*, and *Neisseria meningitidis*) account for most cases of acute bacterial meningitis in neonates and children, although the reasons for this association remain incompletely understood.

The absence of an opsonic or bactericidal antibody is a major risk factor in most cases of meningitis caused by group B streptococcus, *E coli*, Hib, *S pneumoniae*, and *N meningitidis*.[8–12] Age-related incidence of Hib and *N meningitidis* disease is inversely related to prevalence of serum bactericidal activity,[8,10] and the lack of type-specific antibody is a major risk factor for neonatal group B streptococcal disease.[11] Determinations of microbial targets capable of inducing opsonic or bactericidal antibodies and successful vaccination programmes with such targets in infants and children have changed the epidemiology of bacterial meningitis.[13–18] However, microbial targets for opsonic or bactericidal antibodies have not been determined against all pathogens that commonly cause meningitis.

The advancement of vaccine design in enhancing immunogenicity has been shown to be important in preventing meningitis caused by Hib, *S pneumoniae*, and *N meningitidis*. Protein-conjugated capsular poly-saccharide vaccines have almost completely eliminated meningitis caused by vaccine serotypes. Routine immunisation in young infants and children with Hib conjugate vaccines has virtually eradicated meningitis due to these organisms in many high-income countries;[13] in the USA, Hib meningitis happens primarily in children that are not immunised and among infants too young to have completed the primary immunisation series.[14] Additionally, introduction of the seven-valent pneumococcal conjugate vaccine (PCV7) has led to a substantial reduction in the incidence of pneumococcal meningitis in infants and children younger than 5 years.[15–17] Use of these protein-conjugated vaccines has also reduced Hib and pneumococcal meningitis among unvaccinated populations through herd immunity. At present, limitations with PCV7 and meningococcal conjugate vaccines include an apparent increase in the incidence of invasive pneumococcal disease, including meningitis caused by non-PCV7 serotypes, such as serotype 19A (a penicillin and third-generation cephalosporin-resistant non-PCV7 serotype), and an apparent decline in bactericidal antibody against *N meningitidis* in infants, requiring a booster immunisation in the second year of life.[17,18]

Pathogenesis

A relatively small number of microbial pathogens has been shown to account for most cases of meningitis in infants and children, but how those pathogens cross the blood–brain barrier and cause meningitis is incompletely
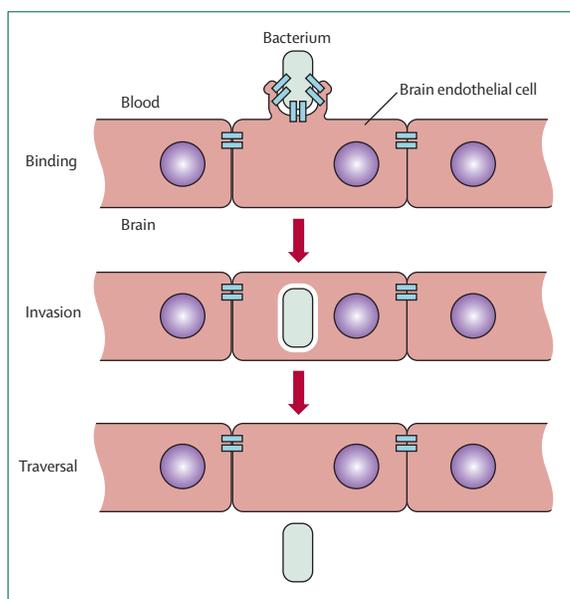
Figure: **Bacterial interaction with the blood–brain barrier, contributing to penetration into the brain**

understood.[7,19] Experimental animal models and human cases of meningitis suggest that *E coli* and group B streptococcus penetrate the brain initially through the cerebral vasculature.[20–23] The blood–brain barrier is a structural and functional barrier that is formed by brain microvascular endothelial cells,[24] which protects the brain from any microbes and toxins circulating in the blood. However, meningitis-causing pathogens, including *E coli*, group B streptococcus, *S pneumoniae*, and *N meningitidis*, have been shown to cross the blood–brain barrier as live bacteria.[7,19,25–29]

Meningitis-causing pathogens cross the blood–brain barrier transcellularly, paracellularly, or by means of infected phagocytes (so-called Trojan horse mechanism).[19] Transcellular traversal of the blood–brain barrier has been shown for most meningitis-causing pathogens in infants and children, including *E coli*, group B streptococcus, and *S pneumoniae* (figure).[7,19,25–28]

Recent studies have shown that microbial traversal of the blood–brain barrier happens via microbial interactions with host receptors (table 1).[7,19,25–29] For example, *E coli* penetration into the brain involves its binding to and invasion of the human brain microvascular endothelial cells (HBMEC) that constitute the blood–brain barrier.[7,19] The *E coli* proteins that contribute to HBMEC binding (ie, FimH and OmpA) do so through interactions with their respective HBMEC receptors, CD48 and endoplasmin (formerly gp96).[30,47–49] Endoplasmin is an endoplasmic reticulum paralogue of heat shock protein 90 that is also present on the surface of HBMEC.[30] In addition, it acts as a cellular receptor for *L monocytogenes* Vip, which is involved in infection of the spleen, liver, and brain of mice.[31] However,

endoplasmin also interacts with OmpA, affecting different host signalling molecules.[30,31]

E coli invasion of HBMEC has also been shown to happen through other interactions with host receptors.[7,19,25,50–52] For example, cytotoxic necrotising factor 1 (CNF1) interacts with 40S ribosomal protein subunit A (RPSA) on HBMEC.[32,53] The monomer of RPSA (37 kDa laminin receptor protein) is a ribosome-associated cytoplasmic protein and a precursor of the 67 kDa laminin receptor. It is unclear how the laminin receptor is matured and synthesised from the laminin receptor protein, but the mature monomer is shown to be present on the cell surface and functions as a membrane receptor for the adhesive basement membrane protein laminin.[54] RPSA has also been shown to be a cellular target for various CNS-infecting microorganisms (table 1), including *S pneumoniae*, *N meningitidis*, Hib, dengue virus, adeno-associated virus, Venezuelan equine encephalitis virus, and prion protein.[33–37] The mechanism by which the same receptor is involved in CNS penetration by different organisms remains to be established.

Other meningitis-causing pathogens, such as group B streptococcus and *L monocytogenes*, possess several microbial structures that allow their binding to and invasion of HBMEC. Group B streptococcal binding to HBMEC happens via Lmb (laminin-binding protein), FbsA (fibrinogen-binding protein), pili, and IagA (via lipoteichoic acid anchoring),[22,38,55,56] but whether these structures are unique to meningitis isolates of group B streptococcus is unclear. *L monocytogenes* invasion of HBMEC is mediated by internalin B (InlB).[42] Several HBMEC receptors for InlB have been identified, which include the receptor for the globular head of complement component C1q (gC1q-R) and Met tyrosine kinase,[57,58] but their contributions to *L monocytogenes* invasion of HBMEC remain incompletely understood. For example, InlB does not compete for the same interaction site on Met tyrosine kinase as the natural ligand, hepatocyte growth factor.[59] gC1q-R is also the HBMEC receptor for *Plasmodium falciparum*-infected erythrocytes (table 1).[41] *L monocytogenes* penetration into the CNS has been attributed to transmigration of *L monocytogenes*-infected monocytes and myeloid cells across the blood–brain barrier,[60,61] although the main route of *L monocytogenes* penetration into the CNS still needs to be determined.

S pneumoniae crosses the blood–brain barrier partly through interaction between cell-wall phosphorylcholine and the platelet-activating factor receptor (PAFR), as shown by partial inhibition of pneumococcal invasion of HBMEC by a PAFR antagonist,[28,39] and delayed translocation of pneumococci from the lung to the blood and from the blood to the cerebrospinal fluid (CSF) in PAFR-knockout mice.[62] PAFR has also been shown to interact with Hib (table 1),[40] but its contribution to Hib traversal of the blood–brain barrier is unclear.

N meningitidis invasion of HBMEC is mediated by the outer membrane protein Opc binding to fibronectin,

	Ligands	References
Endoplasmin		
Escherichia coli	OmpA	30
Listeria monocytogenes	Vip	31
37 kDa laminin receptor protein		
Escherichia coli	CNF1	32
Neisseria meningitidis	PilQ/PorA	33
Streptococcus pneumoniae	CbpA	33
Hib	Omp2	33
Prion protein	..	34
Viruses (sindbis, dengue, tick-borne encephalitis, Venezuelan equine encephalitis, adeno-associated)	..	35–38
Platelet-activating factor receptor		
Streptococcus pneumoniae	Phosphorylcholine	39
Hib	Phosphorylcholine	40
gC1q-R		
Plasmodium falciparum	Infected erythrocytes	41
Listeria monocytogenes	InlB	42
CD46		
Neisseria meningitidis	Pili	43
Measles	Haemagglutinin	44
Adenovirus	Ad35 knob	45
Human herpesvirus 6	Glycoprotein H	46

CNF1=cytotoxic necrotising factor 1. gC1q-R=receptor for the globular head of complement component C1q. Hib=*Haemophilus influenzae* type b.

Table 1: Blood–brain barrier receptors used by CNS-infecting microorganisms

thereby anchoring the bacteria to the integrin $\alpha_5\beta_1$ receptor on the cell surface.[29] In addition, *N meningitidis* pili bind to CD46 on HBMEC,[43] and lipo-oligosaccharides have been shown to contribute to a high-degree of bacteraemia and subsequent penetration into the CNS.[63] CD46 has also shown to be a receptor for measles, adenovirus, and human herpesvirus 6 (table 1).[44–46]

The involvement of host receptors and signal-transduction pathways in the microbial invasion of the blood–brain barrier might provide a new way to prevent and treat meningitis by the targeting of such host receptors or signalling molecules.[7,19,64–69] A proof-of-concept study has shown that down-modulation of the HBMEC receptor for CNF1 (RPSA) and blockade or inhibition of host molecules involved in *E coli* invasion of HBMEC (eg, cytosolic phospholipase A2α) were efficient in preventing *E coli* penetration into the brain.[19,32,53,64] Recent studies suggest that this concept is also relevant to other meningitis-causing pathogens,[19,33,64] and could indeed be used to prevent or treat meningitis.

Of note, the mechanisms involved in microbial invasion of the blood–brain barrier differ from those involved in the release of cytokines and chemokines in response to meningitis-causing pathogens. For example, interleukin-8 secretion in response to *E coli* strain K1 happens in HBMEC, but not in non-brain endothelial cells (eg, human umbilical vein endothelial cells). However, *E coli* proteins involved in binding to and invasion of HBMEC did not affect the release of interleukin 8 from HBMEC.[70] Similar findings were seen for a group B streptococcus Lmb mutant, which was defective for the invasion of HBMEC, but induced equal concentrations of interleukin 8 compared with the parent strain.[38] In addition, *N meningitidis* invasion of HBMEC has been shown to involve c-Jun kinases 1 and 2, although the release of interleukins 6 and 8 from HBMEC in response to bacterial invasion involves the p38 mitogen-activated protein kinase pathway.[68] These findings suggest that targets for prevention of bacterial penetration into the brain differ from those involved in CNS inflammation associated with meningitis.

Diagnosis
Clinical findings
Bacterial meningitis requires early diagnosis and empirical antimicrobial treatment. However, the symptoms and signs depend on the age of the child, the duration of illness, and the host response to infection. The clinical features of bacterial meningitis in infants and children can be subtle, variable, non-specific, or even absent. In infants, they might include fever, hypothermia, lethargy, irritability, poor feeding, vomiting, diarrhoea, respiratory distress, seizures, or bulging fontanelles. In a study of neonatal meningitis, fever or hypothermia was noted in 62% of cases.[71] In older children, clinical features might include fever, headaches, photophobia, nausea, vomiting, confusion, lethargy, or irritability.

Other signs of bacterial meningitis on physical examination include Kernig's sign (flexing the hip and extending the knee to elicit pain in the back and legs), Brudzinski's sign (passive flexion of the neck elicits flexion of the hips), focal neurological findings, and increased intracranial pressure. Signs of meningeal irritation are present in 75% of children with bacterial meningitis at the time of presentation.[72] By contrast, in a retrospective review of 326 children presenting to a paediatric emergency department in the Netherlands between 1988 and 1998 with signs of meningeal irritation, 30% had bacterial meningitis.[73] Absence of meningeal irritation in children with bacterial meningitis was substantially more common in those younger than 12 months.[74] The constellation of systemic hypertension, bradycardia, and respiratory depression (Cushing's triad) is a late sign of increased intracranial pressure.

Laboratory findings
CSF examination is of paramount importance for the diagnosis of all forms of meningitis (table 2). Patients with suspected meningitis should receive a lumbar puncture after a mass lesion has been ruled out on clinical grounds or by CT scan of the head, and if there is no cardiopulmonary compromise. Evidence for mass

lesions will include focal neurological signs and evidence of increased intracranial pressure, and CSF pressure should be recorded during the lumbar puncture.

A Gram stain of CSF will show whether bacteria are present, and a positive Gram stain shows bacterial counts higher than 1×10^3 cells per mL in CSF.[75–78] Gram stain is positive in about 90% of children with pneumococcal meningitis, about 80% of children with meningococcal meningitis, half of patients with Gram-negative bacillary meningitis, and a third of patients with listeria meningitis.[75–78] Cytospin centrifugation increases the chances of detecting organisms in Gram-stained CSF.[79] CSF cell count and differential, and concentrations of protein and glucose are helpful in the differential diagnosis of various forms of meningitis (table 2). A low CSF white blood cell count with positive Gram stain is a risk factor for an unfavourable outcome.[6]

CSF culture can be negative in children who receive antibiotic treatment before CSF examination. For example, complete sterilisation of *N meningitidis* from CSF happened within 2 h of giving a parenteral third-generation cephalosporin and the beginning of sterilisation of *S pneumoniae* from CSF by 4 h into treatment.[80] In such children, increased CSF white blood cell counts and increased CSF protein concentration are usually sufficient to establish the diagnosis of bacterial meningitis. Blood cultures or non-culture diagnostic tests might help in identifying the infecting pathogen.

Non-culture methods

Non-culture tests should be considered for patients who need earlier identification of pathogens or have previously received antibiotics, or whose initial CSF Gram stain is negative with negative culture at 72 h incubation. Such tests include latex agglutination, PCR, loop-mediated isothermal amplification method, microarray or biochip, and immunochromatography (table 3).

Latex agglutination uses latex beads adsorbed with microbe-specific antibodies. In the presence of homologous antigen there is visible agglutination of the antibody-coated latex beads. Latex agglutination assays have been sensitive towards Hib antigen, but less sensitive with *N meningitidis* antigen.[78,81] In the multicentre pneumococcal meningitis surveillance study, latex agglutination was positive in 49 (66%) of 74 CSF samples that grew *S pneumoniae*, and in four of 14 CSF samples that were culture-negative.[6]

The use of standard or sequential-multiplex PCR has been shown to be useful in identification of infecting pathogens in patients who have previously received antibiotics or in resource-poor settings.[82–87] Multiplex real-time PCR or broad-range PCR aimed at the 16S ribosomal RNA gene of eubacteria is promising for the detection of pathogens from CSF. The detection rate was substantially higher with PCR than with cultures in patients who had

	Opening pressure (cm H$_2$0)	White blood cells (×10^6 cells per L)	Glucose (mg/dL)	Protein (mg/dL)
Bacteria*				
Common	>20	>1000	<10	>100
Less common	<20	5–1000	10–45	50–100
Mycobacterium tuberculosis				
Common	>20	100–500	10–45	>100
Less common	<20	5–100	<10	50–100
Borrelia burgdorferi				
Common	<20	100–500	10–45	50–150
Less common	<20	5–100	<10	>150
Treponema pallidum				
Common	<20	5–500	10–45	50–150
Less common	<20	>500	<10	>150
Fungi				
Common	Variable	5–500	10–45	>100
Less common	Variable	>500	<10	50–100
Viruses				
Common	<20	5–500	Normal	50–100
Less common	<20	>500	10–45	>100

*Group B streptococci, *Escherichia coli*, *Listeria monocytogenes*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b.

Table 2: **Likely pathogens for CNS infections on the basis of cerebrospinal fluid analysis**

previously received antibiotics.[82] However, the limit of detection differs between assays. Real-time PCR has been shown to detect as few as two copies of *E coli*, *N meningitidis*, and *S pneumoniae*, 16 copies of *L monocytogenes*, and 28 copies of group B streptococcus,[82] whereas the sensitivity for broad-range 16S ribosomal DNA PCR was about 10–200 organisms per mL CSF.[84,85] The time needed for the whole process from DNA extraction to the end of real-time PCR was 1·5 h,[82] an attractive timeframe for its application in clinical practice.

A Gram-stain-specific probe-based real-time PCR using 16S ribosomal RNA has been shown to allow simultaneous detection and discrimination of clinically relevant Gram-positive and Gram-negative bacteria directly from blood samples,[86] which might provide more rapid and accurate diagnosis of bacterial infection in infants and children. In addition, sequential PCR-based serotyping of *S pneumoniae* using serotype-specific primers could improve ascertainment of pneumococcal serotype distribution in settings in which prior use of antibiotics is high.[87]

A recently developed nucleic-acid amplification technique, loop-mediated isothermal amplification, which amplifies DNA under isothermal conditions (63°C), is a promising tool, particularly in resource-poor settings, because it does not need thermocycling apparatus and the results can be read with the naked eye (based on turbidity or colour development by SYBR Green dye for

	Clinical application	Comments
Latex agglutination[78,81]	Yes	Sensitive with *Haemophilus influenzae* type b, but less sensitive with *Neisseria meningitidis*
PCR[82–87]	Not yet	Need to develop specific and broad targets or primers
Loop-mediated isothermal amplification[88,89]	Not yet	Does not require thermocycling apparatus; potentially useful in resource-poor settings
Microarray or biochip[90–92]	Not yet	Requires a suitable biochip
Immunochromatography[93]	Not yet	Highly sensitive for *Streptococcus pneumoniae*

Table 3: Non-culture diagnostic tests for identification of pathogens for meningitis

staining nucleic acids).[88,89] The assay detected ten or more copies of *S pneumoniae* in oral mucosa swab samples,[88] but its use in the diagnosis of bacterial meningitis has not been tested.

Identification of pathogens by use of a microarray or biochip involves extraction of genomic DNA from CSF, amplification of targeted DNA, and hybridisation of labelled DNA with oliogonucleotide probes (pathogen-specific or virulence genes) immobilised on a microarray.[90–92] However, its usefulness in clinical practice has not been shown.

A rapid immunochromatographic test for *S pneumoniae* was evaluated in 122 children with pneumococcal meningitis.[93] Compared with CSF culture (sensitivity of 71%) and latex agglutination (86%), immuno-chromatography was 100% sensitive for the diagnosis of pneumococcal meningitis, suggesting that immuno-chromatography might be useful in the diagnosis of pneumococcal meningitis.

Bacterial meningitis score

The ability to distinguish between bacterial and non-bacterial aseptic meningitis in infants and children in the emergency department could contribute to limiting hospital admissions or unnecessary use of antibiotics. The bacterial meningitis score has been developed for assessing infants and children with meningitis, and outpatient management might be considered for children who had pleocytosis (7×10^6 cells per L or more) and none of the following five criteria on presentation: history of a seizure with the illness, blood neutrophil count of at least 10×10^9 cells per L, positive CSF Gram stain, CSF protein of at least 80 mg/dL, or CSF neutrophil count of at least 1×10^9 cells per L. However, this proposed diagnostic tool only achieved 95% sensitivity.[94,95] For example, five patients with bacterial meningitis who had pleocytosis were found to have a bacterial meningitis score that indicated low risk, and 5·5% of meningitis cases happened without pleocytosis.[95] Because bacterial meningitis is defined as inflammation that happens in response to bacteria and bacterial products, patients with CSF culture positivity without pleocytosis or increased CSF protein concentrations are presumably representative of the early stages of bacterial meningitis.[7]

Antimicrobial treatment

Eradication of the infecting organism from the CSF is entirely dependent on antibiotics, and bactericidal antibiotics should be administered intravenously at the highest clinically validated doses to patients with suspected bacterial meningitis.[96,97] Several retrospective and prospective studies showed that delay in antibiotic treatment was associated with adverse outcomes.[98–101] In patients with suspected bacterial meningitis for whom immediate lumbar puncture is delayed due to pending brain imaging study or the presence of disseminated intravascular coagulation, blood cultures must be obtained and antimicrobial treatment should be initiated immediately. Selection of empirical anti-microbial regimens is designed to cover the likely pathogens, based on age of the patient and specific risk factors (table 4), with modifications if CSF Gram stain is positive.

The ability of an antimicrobial agent to penetrate the blood–brain barrier is the most important factor that determines whether efficient bacterial killing happens in the CSF. Blood–brain-barrier penetration is affected by lipophilic property, molecular weight, and protein-binding ability of drugs, inflammation of the meninges, and efflux transporters.[102,103] Lipophilic agents (ie, fluoroquinolones and rifampicin) penetrate relatively well into the CSF even if the meninges are not inflamed, whereas hydrophilic agents (ie, β-lactams and vancomycin) have decreased penetration into CSF in the absence of meningeal inflammation.[102–104]

An important factor in the choice of empirical antimicrobial agents is the emergence of antimicrobial-resistant organisms, including *S pneumoniae* that is resistant to penicillin or third-generation cephalosporins, and Gram-negative bacilli that are resistant to many β-lactam drugs. For example, the prevalence of *S pneumoniae* strains that are relatively resistant to penicillin (minimum inhibitory concentration [MIC] 0·1–1·0 μg/mL) or highly resistant to penicillin (MIC greater than 1·0 μg/mL) is increasing, and many of the penicillin-resistant pneumococci have reduced susceptib-ility to third-generation cephalosporins (ie, cefotaxime and ceftriaxone).[96,97] Treatment failures in bacterial meningitis as a result of multiresistant organisms have been reported.[105] Therefore, empirical treatment for patients with bacterial meningitis in areas where resistant *S pneumoniae* strains are prevalent must include the addition of vancomycin (panel). However, penetration of vancomycin into the CSF can be reduced in the absence of meningeal inflammation and also in patients who receive adjunctive dexamethasone treatment.

Treatment of patients at risk of infection with *L monocytogenes* must include a synergistic regimen containing ampicillin and an aminoglycoside (eg, gentamicin), whereas a regimen for Gram-negative bacilli with a high likelihood of resistance (eg, nosocomial meningitis) should include an aminoglycoside (eg,

amikacin) plus a third-generation or fourth-generation cephalosporin, or meropenem. The penetration of intravenously given aminoglycosides into the CSF remains variable or poor even in the presence of meningeal inflammation, and thus cannot be used as monotherapy for bacterial meningitis.[106]

Antibacterial killing activity in CSF also depends on the bacterial burden at the start of treatment. The MIC and minimum bactericidal concentration are established in laboratories by use of bacterial inoculum size of 10^4–10^5 organisms per mL. However, some patients with bacterial meningitis (eg, caused by group B streptococcus and *S pneumoniae*) who have many organisms on CSF Gram stain are likely to yield 10^7–10^8 organisms per mL,[6,76] and MIC values can be 100–1000-times higher than would normally be expected. For example, MICs of β-lactam antibiotics, including penicillin against group B streptococcus, were increased 1000 times when the inoculum size increased from 10^4 to 10^8 organisms per mL.[107] Careful monitoring of the response to antimicrobial treatment is therefore warranted for patients with bacterial meningitis who have high bacterial burden on the basis of initial CSF Gram stain.

Antimicrobial susceptibility patterns must be established for all organisms isolated from the CSF. For example, group B streptococcus is commonly responsible for neonatal bacterial meningitis, and has been shown to be uniformly susceptible to β-lactam antibiotics (eg, penicillin MIC 0·1 μg/mL or less), and thus penicillin is at present the drug of choice for invasive group B streptococcal infection including meningitis.[108] However, studies have reported isolates of group B streptococcus with penicillin MICs of 0·12–1·0 μg/mL that had mutations in the target penicillin-binding proteins similar to the mechanisms involved in penicillin-resistant *S pneumoniae*.[109,110] The optimum empirical regimen for meningitis caused by penicillin non-susceptible group B streptococci that includes third-generation cephalosporins has not been established.

Similarly, penicillin has been the standard treatment for meningococcal meningitis, but penicillin resistance has evolved, with an implication of treatment failures.[111,112] A recent study in Spain reported an increased incidence in penicillin non-susceptible strains of *N meningitidis* (eg, MICs 0·1–0·5 μg/mL) from 9·1% in 1986 to 71·4% in 1997.[113] By contrast, relative resistance to penicillin (MIC 0·1 μg/mL) has been shown to occur in 3–4% of the meningococcal isolates in the USA and in 2% of the 137 isolates recovered between 2000 and 2006 from equatorial sub-Saharan Africa (the so-called meningitis belt).[114,115] These findings support the use of a third-generation cephalosporin for meningococcal meningitis in areas where penicillin resistance is prevalent, at least until penicillin susceptibility is known.

The potential roles of newer β-lactam antibiotics (meropenem, cefepime, ertapenem), recently developed quinolones (moxifloxacin, gatifloxacin, gemifloxacin,

	Likely pathogens
<1 month	Group B streptococci, *Escherichia coli*, *Listeria monocytogenes* (neonatal pathogens)
1–3 months	
No immunisation or one dose of primary immunisation	*Neonatal pathogens*, *S pneumoniae*, *N meningitidis*, Hib
3–6 months	
No immunisation	*S pneumoniae*, *N meningitidis*, Hib
At least two doses of primary immunisation (with Hib-Omp vaccine)	*S pneumoniae*, *N meningitidis*
>7 months to 5 years	
No immunisation	*S pneumoniae*, *N meningitidis*, Hib
Primary immunisation completed	*S pneumoniae* (non-PCV serotypes), *N meningitidis*
6–21 years	*S pneumoniae*, *N meningitidis*

Risk factors for specific pathogens are as follows: cerebrospinal fluid leak, cochlear implant, nephrotic syndrome (*Streptococcus pneumoniae*); terminal complement deficiencies, freshmen living in dormitories, outbreaks (*Neisseria meningitidis*); asplenia, sickle-cell disease, HIV infection, otitis, sinusitis (*S pneumoniae*, *Haemophilus influenzae* type b [Hib]); immunodeficiency, diabetes mellitus (*S pneumoniae*, *Listeria monocytogenes*). PCV=pneumococcal conjugate vaccine.

Table 4: **Likely pathogens for meningitis based on age and immunisation status**

garenoxacin), and lipopeptides (daptomycin) in the treatment of meningitis caused by resistant bacteria have been shown in animal models of experimental meningitis.[102,106,116–124] For example, gatifloxacin was as effective as the combination of ceftriaxone and vancomycin against a highly cephalosporin-resistant pneumococcal strain in an experimental meningitis model.[120] Moxifloxacin and garenoxacin had CSF bacterial killing rates that exceeded those found with the combination of ceftriaxone and vancomycin against experimental meningitis caused by vancomycin-tolerant *S pneumoniae*.[124] However, clinical effectiveness of these newer antimicrobial drugs as monotherapy in the treatment of meningitis caused by penicillin non-susceptible isolates of *S pneumoniae* has not been established, but they might be useful if other drugs cannot be used, and continued monitoring of antimicrobial susceptibility patterns, including newer agents, is thus important. Of interest, dexamethasone did not substantially affect the penetration of gemifloxacin and moxifloxacin into the CSF.[119,121] Fluoroquinolones are not recommended for use in children younger than 18 years because of concerns about their effects on growing cartilage in experimental animals.[125]

Adjunctive treatment

Neurological sequelae are common in survivors of meningitis, and include hearing loss, cognitive impairment, and developmental delay. For example, the Metropolitan Atlanta Developmental Disabilities Surveillance Program in 1991 identified bacterial meningitis as the leading postnatal cause of developmental disabilities, including cerebral palsy and mental retardation.[126] Hearing loss happens in 22–30% of survivors of pneumococcal meningitis compared to 1–8% after meningococcal meningitis.[6,96,97,127]

In a 2007 Cochrane review, adjunctive treatment with dexamethasone was associated with lower case mortality, and lower rates of severe hearing loss and long-term neurological sequelae.[128] The beneficial effect of adjunctive dexamethasone treatment was evident in adults with bacterial meningitis. Dexamethasone given shortly before or when antibiotics were first given has been shown to reduce the rate of hearing loss in children with Hib meningitis, but its beneficial effects on hearing and other neurological sequelae are not as clear against meningitis caused by other organisms.[6,129] The American Academy of Pediatrics Committee on Infectious Diseases suggests that dexamethasone treatment might be considered for infants and children older than 6 weeks with pneumococcal meningitis after considering the potential benefits and possible risks.[130]

The widespread use of dexamethasone in children with bacterial meningitis needs careful monitoring of clinical (eg, fever curve, resolution of symptoms and signs) and bacteriological responses to antimicrobial treatment, particularly for patients with meningitis caused by pneumococci that are resistant to third-generation antibiotics, in whom bacteriological killing in the CSF depends on vancomycin. Monitoring of the clinical response (eg, fever curve) can be complicated by the use of dexamethasone. For example, secondary fever (recurrence of fever after at least 24 h without fever) happens more commonly in patients treated with dexamethasone than in those who are not (52% vs 24%, p=0·0009).[6] In addition, concomitant giving dexamethasone and vancomycin can reduce penetration of vancomycin into the CSF by virtue of the anti-inflammatory activity of dexamethasone, resulting in treatment failure.[131] However, CSF bactericidal activity has been shown in children who have meningitis due to cephalosporin-resistant pneumococci, and such cases should be treated with dexamethasone as well as vancomycin and ceftriaxone.[132]

Another issue with adjunctive dexamethasone treatment is the possibility of neuronal injury, including hippocampal apoptosis in experimental animals with pneumococcal and *E coli* meningitis who received dexamethasone.[133,134] Long-term follow-up studies are thus needed to address the effect of dexamethasone treatment on any cognitive and neuropsychological outcomes in patients with bacterial meningitis.

A recent multicentre, double-blind randomised study in six Latin American countries showed that adjunctive treatment with oral glycerol (1·5 g/kg every 6 h for 48 h) prevents severe neurological sequelae in childhood meningitis (odds ratio 0·31; 95% CI 0·31–0·76) compared with placebo.[135] Glycerol is a hyperosmolar agent, and because of its safety, wide availability, low cost, and oral administration, its use as adjunctive treatment in children with bacterial meningitis, particularly in resource-limited settings, is promising.

Future challenges

Bacterial meningitis continues to be an important cause of mortality and morbidity throughout the world, particularly for those infections in newborns, individuals living in low-income countries, and infections caused by antimicrobial-resistant pathogens (eg, cephalosporin-resistant pneumococcus) or organisms that are difficult to treat (eg, multi-resistant Gram-negative bacilli). Success with the protein-conjugate Hib and *S pneumococcus* PCV vaccines in the prevention of meningitis shows that identification of conserved targets for opsonic or bactericidal antibodies is likely to enhance the development of effective vaccination programmes for the prevention of meningitis caused by *N meningitidis* and other meningitis-causing bacteria. Advances in microbial genome sequencing and functional genomic approaches are likely to be beneficial in the identification of such microbial targets.

Emergence of antimicrobial-resistant bacteria presents a constant challenge to the development of new bactericidal antibiotics for the treatment of bacterial meningitis. Another important consideration for the treatment of bacterial meningitis is the substantial morbidity in survivors of meningitis; effective strategies to prevent morbidity are lacking at present, partly because of our incomplete knowledge on the pathogenesis of neurological sequelae associated with bacterial meningitis.

New information available on the pathogenesis of meningitis is likely to be useful for the prevention and treatment of bacterial meningitis. Most meningitis-causing pathogens cross the blood–brain barrier, involving specific interactions of microbial structures

Search strategy and selection criteria

The information for this Review was identified by searches of Medline in June, 2009 (date limits January, 2000, to June, 2009), with the following search terms (alone and in combination): "neonatal bacterial meningitis", "bacterial meningitis in infants and children", "pathogenesis of bacterial meningitis", "microbial invasion and/or traversal of the blood–brain barrier", "diagnosis of bacterial meningitis", "treatment of bacterial meningitis", and "adjunct therapy of bacterial meningitis", with the emphasis on new information reported since 2000. Earlier original articles were also included, which formed the foundation for subsequent studies. Only papers published in English were considered.

with the host receptors, and eliciting host signalling molecules. Blockade or inhibition of such host receptors or signalling molecules is efficient in preventing microbial traversal of the blood–brain barrier, and this host-based approach presents a new approach in our strategies to prevent and treat bacterial meningitis.

Conflicts of interest
I declare that I have no conflicts of interest.

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