Acute Bacterial Meningitis in Infants and Children
Epidemiology and Management

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Contents

Abstract

Acute bacterial meningitis (ABM) continues to be associated with high mortality and morbidity, despite advances in antimicrobial therapy. The causative organism varies with age, immune function, immunization status, and geographic region, and empiric therapy for meningitis is based on these factors. *Haemophilus influenzae* type b *(Hib), Streptococcus pneumoniae*, and *Neisseria meningitidis* cause the majority of cases of ABM.

Disease epidemiology is changing rapidly due to immunization practices and changing bacterial resistance patterns. Hib was the leading cause of meningitis in children prior to the introduction of an effective vaccination. In those countries where Hib vaccine is a part of the routine infant immunization schedule, Hib has now been virtually eradicated as a cause of childhood meningitis. Vaccines have also been introduced for pneumococcal and meningococcal diseases, which have significantly changed the disease profile. Where routine pneumococcal immunization has been introduced there has been a reported increase in invasive pneumococcal disease due to non-vaccine serotypes.

In those parts of the world that have introduced conjugate meningococcal vaccines, there has been a significant change in the epidemiology of meningococcal meningitis. As a part of the United Nations Millennium Development Goal 4, the WHO has introduced a new vaccine policy to improve vaccine availability in resource poor countries.

In addition, antibiotic resistance is an increasing problem, especially with pneumococcal infection. Effective treatment focuses on early recognition and use of effective antibiotics.

This review will attempt to focus on the changing epidemiology of ABM in pediatric patients due to vaccination, the changing patterns of infecting bacterial serotypes due to vaccination, and on antibiotic resistance and its impact on current management strategies.

Acute bacterial meningitis (ABM) remains a serious global health threat with high mortality and morbidity, despite advances in antibiotic therapy and modern vaccination strategies. Children are particularly vulnerable to ABM because of their relatively immature immune systems, particularly their impaired immunity to the polysaccharide capsule of bacteria commonly associated with ABM.[1] It has been estimated that over 75% of all cases of ABM occur in children under 5 years of age, and it is one of the most common life-threatening infections in children worldwide.

The WHO estimates that about 170 000 deaths occur annually from the disease worldwide; the case fatality rate can be as high as 50% if not treated.[2,3] The estimated median risk of at least one major or minor sequela from ABM after hospital discharge is 19.9% (range 12.3–35.3%).[4] Adverse outcome varies with age group, geographic location and the infecting organism. In middle- and low-income countries, ABM remains the fourth leading cause of disability.[4]

This review focuses on the changing disease epidemiology of ABM following the widespread introduction of vaccines effective in young infants, where the greatest disease burden lies, and their impact on bacterial serotypes causing disease. It also focuses on emerging antimicrobial resistance and its influence on ABM treatment.

1. Epidemiology of Acute Bacterial Meningitis

The incidence of ABM worldwide is difficult to ascertain because of wide variation in surveillance in different regions of the world, together with underreporting from many developing nations. The incidence has decreased to 1–3 cases per 100 000 population per year in the developed world.[5-7] During pandemic meningococcal meningitis in Sub-Saharan Africa, attack rates exceed 100–800 cases per 100 000 population per year, with the highest attack rates reaching as high as 1 in 100.[8]

Most of the human pathogenic bacteria can cause meningeal infection, but three bacterial species, namely *Haemophilus influenzae* type b *(Hib)*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*, are responsible for over 90% of reported ABM cases in the world beyond the neonatal period.[4] The epidemiology of ABM has changed dramatically in the last two decades with the introduction of new, highly effective vaccines. Prior to introduction of the conjugate polysaccharide vaccine against Hib, Hib was the most common cause of ABM worldwide.[9] More recently, *S. pneumoniae* and *N. meningitidis* have become the most common causes of ABM due to decline in the incidence of Hib meningitis following the introduction of Hib vaccine.[9] International efforts to tackle the problem have taken a new direction since recent epidemiologic data revealed that Hib and pneumococcus are directly responsible for as many child deaths as HIV/AIDS, malaria and tuberculosis together.[4]

Causative organisms of ABM vary according to the population studied, age of the study group, and geographic area studied. Table I lists the causes of ABM according to age and underlying conditions. The microbial epidemiology of meningitis is also changing in older children and adults, in whom nosocomial meningitis accounts for an increasing proportion of infections. Many of these are associated with recent neurosurgical intervention or trauma. In such cases, *Pseudomonas aeruginosa*, enterococci, *Staphylococcus aureus*, and the coagulase-negative staphylococci are the most common causative organisms.

1.1 *Haemophilus Influenzae* Type b

H. influenzae, a respiratory pathogen that causes invasive disease due to serotype b (Hib), was the most common cause for ABM prior to introduction of the conjugated protein-polysaccharide Hib vaccine in the early 1990s.[9] The introduction of this vaccine has not only resulted in virtual disappearance of invasive Hib disease from industrialized and developing nations, where it is used as part of the routine infant immunization schedule,[10-12] but it has also reduced the carriage of Hib amongst non-vaccinated individuals in these populations.[13,14] Although a highly effective and safe Hib vaccine has been available for nearly 2 decades, and is used as a part of the routine infant immunization schedule in the US, UK, and most countries in Western Europe, vaccine availability in the developing world is still constrained by cost factors.[15,16] The estimated global incidence of Hib meningitis for the year 2000 was 31 cases per 100 000 children younger than 5 years, with a

Table I. Causes of acute bacterial meningitis according to age and underlying condition

Age	Organisms
0–1 mo (neonate)	*Streptococcus agalactiae* (group B Streptococcus)
	Enteric bacilli (*Escherichia coli, Klebseilla pneumoniae, Proteus*)
	Listeria monocytogenes
>1 mo–3 mo	*S. agalactiae* (group B Streptococcus)
	Enteric bacilli (*E. coli, K. pneumoniae, Proteus*)
	L. monocytogenes, Streptococcus pneumoniae, Neisseria meningitidis Hemophilus influenzae type b
>3 mo–5 y	*S. pneumoniae, N. meningitidis, H. influenzae* type b
>5 y–50 y	*S. pneumoniae, N. meningitidis*
>50 y	*S. pneumoniae, N. meningitidis, L. monocytogenes*
	Gram-negative bacilli
Immunocompromised	*S. pneumoniae, N. meningitidis, H. influenzae* type b
	L. monocytogenes, Gram-negative bacilli
	Salmonella species, Enteric bacilli, *Pseudomonas aeruginosa*
Post-neurosurgery, post-skull trauma, cerebrospinal fluid shunt	*S. pneumoniae, N. meningitidis, H. influenzae* type b
	Staphylococcus aureus,
	Coagulase-negative *staphylococci,* Gram-negative bacilli
	Streptococcus pyogenes, Enterococci

case fatality rate of 43% in unimmunized populations.[17] The incidence varies significantly between different regions, from 46 per 100 000 in Africa to 16 per 100 000 in Europe.[17]

The protective efficacy of the Hib conjugate vaccine is 75% (OR 0.25; 95% CI 0.08, 0.84) against meningitis and 69% (OR 0.31; 95% CI 0.10, 0.97) against pneumonia.[18] Surveillance data from European countries where routine Hib immunization is carried out report an incidence of 0.28 per 100 000 population of invasive haemophilus disease in the post-vaccination era, with only 28% of haemophilus isolates being serotype b compared with more than 80% in the pre-vaccination era.[19] There has been no significant increase in invasive non-type b haemophilus disease in these countries since the introduction of Hib vaccine.[19] The global vaccine coverage for Hib in 2009 reported by the Centers for Disease Control and Prevention was only around 30% in infants <12 months of age.[20] Under the United Nations Millennium Development Goal 4 for child mortality

reduction, efforts are ongoing to improve vaccine availability and coverage for resource poor countries. The WHO now recommends the use of Hib and pneumococcal conjugate vaccines as part of routine infant immunization in all countries.[15,21]

1.2 Streptococcus Pneumoniae

S. pneumoniae is an important cause of invasive disease in children <2 years of age, the elderly, and in immunocompromised hosts.[22] Like *H. influenzae*, *S. pneumoniae* spreads from the nasopharynx; the highest rate of *S. pneumoniae* nasopharyngeal carriage is noted in children <6 years of age.[22] Recent estimates suggest 0.7–1 million children die from invasive pneumococcal disease worldwide every year, accounting for 11% of total deaths in non-HIV-infected patients aged <5 years beyond the neonatal period.[21,23] The estimated global incidence of pneumococcal meningitis published by the WHO in 2009 was 17 per 100 000 population in children for the year 2000, with a case fatality rate of 59% (23% in western Pacific regions to 73% in Africa).[24] It is the most severe form of ABM in children, with the highest mortality and morbidity.

A 7-valent pneumococcal conjugate vaccine (PCV7) was introduced for use in children in 2000.[25] The high cost of the vaccine prohibits its use in the routine infant immunization schedule in resource-poor countries. Vaccine efficacy is estimated to be approximately 80% against the seven serotypes included in the vaccine, 58% against all pneumococcal serotypes and 11% for all-cause mortality.[26] The incidence of invasive pneumococcal disease has decreased since the introduction of this vaccine in those countries where it is part of the national immunization schedule, and there is some evidence of herd immunity, as suggested by the decreasing incidence of invasive pneumococcal disease in adults.[25,27,28] The incidence of invasive pneumococcal disease due to vaccine serotypes fell by over 89% since its introduction, and by 63–74% for all serotypes.[29] The most dramatic reduction was reported in White Mountain Apache children <5 years of age, where the rate of disease due to vaccine serotypes decreased from 275 cases per 100 000 in 1991–7 to 0 in 2004–6.[30]

There are 91 distinct serotypes of pneumococcus identified; however, only 20 of these account for >80% of invasive pneumococcal disease.[31] The most common serotypes associated with invasive infection are 14, 4, 1, 6A, 6B, 3, 8, 7F, 23F, 18C, 19F, and 9V.[32,33] The pathogenic serotypes vary depending on age (the majority of childhood disease is caused by serotypes 6, 14, 18C, 19F, or 23F),[32] geographic location (serotypes 1 and 5 are common in developing countries, but rare in the US and Europe),[32,34,35] and organ affected.[33]

There has been a temporal change in the distribution of pathogenic serotypes.[34,35] The serotypes covered in PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F) more commonly cause invasive disease than the non-PCV7 serotypes;[36] however, there has been a reported increase in invasive disease due to non-vaccine serotypes in countries where PCV7 has been introduced into the routine infant immunization schedule.[34,36] Some of the non-PCV7 serotypes, such as 19A, have become more virulent with increased nasopharyngeal carriage; increasing incidence of invasive disease due to serotype 19A has been reported since 2000.[36] This increase has threatened the efficacy of PCV7 and led to the development of vaccines with more inclusive coverage.[36,37] A study from the US showed a decrease of 76% and 94% in invasive disease due to serotypes 6A and 6B, respectively, between 1999 and 2007; however, invasive disease due to serotype 6C, which is not part of PCV7, increased by 164% during the same period (from 0.22 per 100 000 to 0.58 per 100 000).[38]

To counter the increase in non-PCV7 vaccine serotypes, newer vaccines have been developed. These vaccines all include the same seven serotypes as PCV7 as well as other serotypes. A 9-valent conjugate vaccine, which also includes serotypes 1 and 5 in addition to the serotypes present in PCV7, has been found effective in reducing mortality in Gambian children.[39] There are also 10- and 13-valent pneumococcal conjugate vaccines;[40] the 13-valent (PCV13) vaccine has been licensed for use in infants in the US and the UK from 2010 and is expected to further reduce the incidence of invasive pneumococcal disease.[41,42] PCV13 contains an additional six serotypes over and above the PCV7 serotypes, and is likely to cover serotypes that cause 64% of all invasive pneumococcal disease.[43] This vaccine was introduced into the routine infant immunization schedule in the UK in April 2010, replacing PCV7.

The other available pneumococcal vaccine is 23-valent polysaccharide vaccine, which is not suitable for infant vaccination as it is not protein conjugated and thus poorly immunogenic in young children.[44,45] This 23-valent polysaccharide vaccine encompasses most of the penicillin-resistant and macrolide-resistant pneumococcal serotypes and is used to protect patients at high risk of invasive pneumococcal disease (e.g. immunocompromised patients, elderly patients with chronic obstructive pulmonary disease, patients with severe asthma, and patients with splenic dysfunction).[45] Vaccine efficacy is estimated to be 60–80% in adults, although it is somewhat less effective in immunocompromised patients in whom frequent re-vaccination is necessary, which leads to a possible decrease in efficacy. Despite these failings, this vaccine has been effective in decreasing the incidence of invasive pneumococcal disease in adults since its introduction in the 1980s.[46]

The epidemiology of disease due to antibiotic-resistant pneumococci is changing because of selection pressure from antibiotic use, immunization, and the spread of a few international, resistant clones.[22] Some serotypes are specifically associated with increased antimicrobial resistance. For example, since the introduction of PCV7 vaccine in the US, there has been an increase in antimicrobial resistance among non-vaccine serotypes due to a 3-fold increase in the prevalence of *erm(B)* and *mef(A)* isolates of serogroup 19; the relative distribution of 19A serotype has increased since vaccine introduction.[47] These isolates are resistant to the majority of antibiotic classes and are international clonal strains.[47,48] Similarly, there are reports of increasing invasive pneumococcal disease due to non-PCV7 serotypes: the 19A and 6A subtypes in Korea and the 19A subtype in Taiwan.[22] Six serotypes (6A, 6B, 9V, 14, 19F, and 23F) account for more than 80% of penicillin- or macrolide-resistant pneumococci worldwide.[32] There are some multi-drug-resistant clones in select regions, which are worrying and signify the importance of judicious use of antibiotics and development of vaccines with extended serotypic coverage for these drug-resistant organisms.

1.3 Neisseria Meningitidis

N. meningitidis is the leading cause of ABM in the world and is known to cause endemic and epidemic disease, with the greatest burden of disease in children and adolescents. *N. meningitidis* is an obligate human commensal living in the upper respiratory tract. The estimated nasopharyngeal carriage ranges from 0.6% to 34% and is higher in adolescents and individuals living in overcrowded and confined spaces.[49,50] An estimated 500 000 cases of meningococcal disease occur annually worldwide with a case fatality rate of at least 10%.[51] Most cases occur during winter months and early spring. The incidence of endemic disease is 0.5–5 per 100 000 population.[51]

There are at least 13 known serogroups of *N. meningitidis*; however, more than 90% of disease is caused by serogroups A, B, C, W-135, X, and Y.[49] The distribution of serogroups varies with age group and geographic location.[49] Serogroup A causes the highest number of cases and primarily causes large epidemics in the meningitis belt in Sub-Saharan Africa, with an incidence as high as 1 case per 100 population, and a case fatality reaching 75% in children and adolescents.[3,52,53] Serogroup A is much less common in the developed world, although it is found in parts of China and Russia. Serogroup B causes endemic disease in much of the developed world, including the US, Western Europe, Australasia, and South America. Serogroup C is also common in the developed world,

and is occasionally known to cause epidemics and outbreaks.[3,54-56] The incidence of serogroup C disease has decreased in those parts of the world, such as Europe and North America, following the introduction of effective conjugate vaccines against serogroup C; subsequently, serogroup B disease has emerged as the predominant cause of meningococcal disease due to lack of an effective vaccine against this serogroup.[3,52,54] Serogroup Y has become an increasingly important cause of meningococcal disease in the US and serogroup X is becoming more common in parts of Africa.[3]

There are two main types of vaccines used for protection against meningococcal infection: pure polysaccharide vaccines and protein/polysaccharide conjugate vaccines. The polysaccharide quadrivalent vaccine against serogroups A, C, Y, and W-135 is poorly immunogenic in children <2 years of age, and gives temporary immunity for 3–5 years in older people; it does not have any effect on nasal carriage of the bacteria.[52,57,58] Repeated usage may cause immune hypo-responsiveness and should be instituted with caution.[59] More recently, conjugate vaccines have become available against serogroup A, C, Y, and W-135. Conjugate serogroup C vaccine has been introduced successfully into several countries in Europe as a part of the routine immunization schedule in infants.[53,57] This vaccine is not only strongly immunogenic, giving a lasting immune response and immunologic memory, but it also confers herd immunity by decreasing nasal carriage. Since its introduction in the UK in 1999, the incidence of disease due to meningococcal serogroup C has decreased by 94% in immunized populations and 67% in unimmunized populations, and a significant decrease in nasopharyngeal carriage, with no increase in the carriage of other serogroups, has been seen.[60] In the US, a protein conjugate quadrivalent vaccine against serogroups A, C, Y, and W-135 has been licensed since 2005 for routine single-dose immunization in children aged 11–18 years, and in people at high risk of ABM (i.e. immunocompromised individuals, college students living in dormitories, microbiologists or laboratory workers routinely exposed to meningococcal samples, army recruits, close contacts and travelers to meningococcal endemic areas).[61] This vaccine has also been approved for use in 2- to 10-year-olds, but is not a part of the routine immunization schedule in this age group. This is due to concerns regarding adequate lasting response from a dose at 2 years of age, and also because the largest proportion of meningococcal disease in this age group is caused by serogroup B.[62]

As serogroup A meningococcal disease is a major public health concern in the meningitis belt of Sub-Saharan Africa, the WHO initiated a Meningitis Vaccine Project (MVP), which has developed a low-cost conjugate vaccine against serogroup A

(MenAfriVac TM).[3,63] This vaccine has been successfully tested in phase I, II, and III clinical trials and has been launched in mass vaccination campaigns as a single dose to a target population of 250 million people aged 1–29 years across 25 countries in the African meningitis belt. More than 1 million people have already received the vaccine in the region.[3,63]

Serogroup B still remains a common cause of meningococcal septicemia and meningitis, and has accounted for more than 50% of cases in the US[8] and as many as 90% of cases in Europe[64] since the introduction of the MenC vaccine. Serogroup B has a poorly immunogenic capsule,[65] which has hindered progress on developing a vaccine against it. However, vaccines are now being developed targeting non-capsular structures, such as outer membrane porins, vesicles, and lipopolysaccharides.[66-68] An outer membrane vesicle (OMV) vaccine against serogroup B has been recently tested in New Zealand and is reported to have 73% overall efficacy[69] and 80% efficacy in children aged between 6 months and 5 years.[70] The OMV vaccines are useful for control of epidemics because they are directed against specific surface proteins, which are antigenically variable; therefore, the vaccines can be tailored to a predominant strain during an epidemic. However, this does not confer cross-protective immunity against other strains of serogroup B meningococci.[71] Other vaccines against serogroup B containing recombinant human factor H binding protein, along with other components of the bacterial outer membrane or cell wall,[72] are undergoing clinical trials. Further studies are required to prove vaccine efficacy and safety before their widespread use.

1.4 Neonatal Meningitis

Neonates are particularly vulnerable to bacterial infections because of their immature humoral and cellular immunity and phagocytic function.[73] Their inefficient alternative complement pathway compromises their defence against encapsulated bacteria.[74] In addition, preterm infants do not get adequate transplacentally-derived maternal immunoglobulins.[74]

The incidence of neonatal meningitis is approximately 0.3 per 1000 live births in industrialized nations.[75] It is difficult to estimate the incidence in developing countries due to under-developed surveillance systems. Some reports have suggested an incidence as high as 6.1 per 1000 live births in Africa and South Asia.[76] Mortality has decreased significantly in developed countries from nearly 50% in the 1970s to <10% in the last 2 decades;[77] however, long-term complications are still a major cause of concern, especially neuromotor disabilities such as cerebral palsy.[78]

Group B streptococcus (GBS) is the most common cause of neonatal meningitis in the developed world, accounting for

nearly 50% of all cases, followed by *Escherichia coli* (20%) and *Listeria monocytogenes* (5–10%).[79,80] Intrapartum antibiotic prophylaxis in high-risk groups has reduced the incidence of early onset GBS disease, although the incidence of late-onset GBS disease has remained unchanged.[81] Work is ongoing to develop a conjugate GBS vaccine for use in adolescents and pregnant women.[82] There is some evidence to suggest that Gram-negative bacilli, including Klebsiella and *E. coli*, are more common in underdeveloped nations in comparison with developed nations.[77]

1.5 Others

Because of changes in the epidemiology of ABM caused by the above organisms, some other organisms are gaining importance in parts of the world where routine immunization has decreased the incidence of ABM caused by common pathogens. In 2007, the UK Health Protection Agency reported that 13% of ABM in the UK was caused by *Mycobacterium tuberculosis* across all ages.[83]

The exact incidence of tuberculous meningitis is difficult to ascertain because of difficulties with diagnosis and under-reporting, especially in the developing world. The WHO estimates that approximately one-third of the world population is infected with tuberculosis.[84] The incidence is increasing in developed countries due to immigration and increasing HIV infection rates. In the UK there was a 91.9% increase in the incidence of tuberculous meningitis from 1999 to 2006.[85] Similarly, a surveillance study from the US showed an increasing trend towards extrapulmonary tuberculosis from 1993 to 2006.[86] In areas where tuberculosis is highly prevalent, meningitis occurs commonly in children <4 years of age, while in low prevalence areas, most patients with tuberculous meningitis are adults.

Other causes of ABM, for example Gram-negative meningitis or listeria meningitis, are uncommon in immune-competent children beyond the neonatal period and are beyond the scope of this review.

Following trauma and neurosurgical interventions, ABM is predominantly caused by nosocomial infection with organisms such as *Pseudomonas aeruginosa,* enterococci, S*taphylococcus aureus*, and the coagulase-negative staphylococci. Table I lists the causes of ABM according to age and predisposing factors.

2. Treatment

Until the early 20th century, when antibiotics were introduced, ABM was nearly always a fatal disease.[87] The mortality of ABM has subsequently significantly decreased, due to development of effective antibiotics, advancements in intensive care, and introduction of immunization.[88] More recently, antibiotic resistant organisms have emerged because of widespread use of antibiotics and perpetuation of resistant clones in some countries, most notably amongst the pneumococci.[89]

The choice and duration of antimicrobial therapy for ABM depends upon accurate microbiologic diagnosis.[89] The diagnosis is confirmed by obtaining cerebrospinal fluid (CSF), usually by lumbar puncture. Prompt diagnosis is essential, as delay in commencing antimicrobial therapy may increase the likelihood of sequelae or fatalities.[90,91] However, data regarding the use of pre-hospital antibiotics is less convincing because of lack of prospective studies. The latest National Institute for Health and Clinical Excellence (NICE) guidelines from the UK, for the management of bacterial meningitis in children and young people, suggest the use of pre-hospital antibiotics only in suspected meningococcal disease.[92] Appropriate empiric antimicrobial therapy should not be delayed if obtaining a lumbar puncture is likely to take more than 30 minutes.[92,93] Delay in obtaining CSF, for example while awaiting radiologic investigations for patients with atypical neurologic signs, or in those patients where immediate lumbar puncture is contraindicated, may still yield useful information regarding white cell count, protein, and glucose content. In addition, useful microbiologic information may be obtained despite prior antibiotic therapy by the use of latex agglutination for bacterial antigen testing, polymerase chain reaction for bacterial DNA amplification, and from blood cultures.[94-96]

2.1 Antimicrobial Therapy

Most episodes of ABM result from hematogenous spread of the bacteria to the meninges. Once past the blood-brain barrier (BBB), bacterial multiplication is rapid because of the relatively poor host immune response in this site, resulting in large numbers of bacteria (often $>10^6$ colony forming units) per milliliter of CSF.[97] The CSF contains low levels of specific antibody and complement[98] and this results in poor opsonization and phagocytosis. Bacterial capsular polysaccharide is also antiphagocytic.[99]

2.1.1 Principles of Therapy

In experimental meningitis, a peak CSF antibiotic concentration 8- to 10-fold the minimal bactericidal concentration (MBC) for the infecting organism (the lowest concentration of a drug required to kill a pathogen) is required for successful treatment and prevention of relapse.[100,101]

Bactericidal activity of an antibiotic in the CSF is dependent on penetration of the antibiotic across the BBB which, in turn, is related to the physicochemical characteristics of the antibiotic. Small molecular size, low degree of protein binding, high lipid solubility and low degree of ionization at physiologic pH, all increase penetration and concentration of the antibiotic and activity of the antibiotic in the CSF.[102-104]

2.1.2 The Blood-Brain Barrier

The BBB develops increased permeability during meningeal inflammation, with increased vesicular transport across cells in the meningeal arterioles and complete separation of endothelial cell tight junctions.[104-106] However, activity of antibiotics in infected CSF is reduced by the lower pH and raised protein, which reduces the free drug concentration of highly protein-bound antibiotics (such as the cephalosporins).[102-104] Fever may also impair antibiotic effectiveness by reducing bacterial cell wall division, particularly of those antibiotics that bind to bacterial cell-wall components (e.g. β-lactams).[107] Lipophilic agents, such as fluroquinolones and rifampin (rifampicin), have good BBB penetration even in the absence of inflammation, while hydrophilic antibiotics, such as vancomycin and the β-lactams, penetrate the meninges poorly in the absence of meningeal inflammation, and reach peak concentrations more slowly.[104] Aminoglycosides and fluroquinolones are concentration-dependent drugs and their efficacy is defined by high peak concentration and prolonged postantibiotic effect. In contrast, β-lactam antibiotics are concentration-independent drugs and their bactericidal effect depends on the time the concentration exceeds the minimum inhibitory concentration (MIC) for the infecting organism.[102]

2.1.3 Duration and Dosing Interval

The duration and dosing interval of antibiotics in ABM is based upon experience more than evidence. Most of the studies on newer antimicrobials are conducted by comparing the new drug with an established drug in a double-blind setting.[106]

Whether the antibiotics are more effective with intravenous bolus or continuous infusion depends on the organism being treated and the pharmacokinetics of the drug used. In general, intravenous bolus treatment leads to a higher peak concentration, but may not be adequate to maintain CSF concentrations of antimicrobials above the MIC between dosages, while continuous infusion gives a lower peak, but maintains better persistent serum concentrations.[102-104] There is some evidence of continuous ceftriaxone infusion in critically ill patients with sepsis producing clinical and bacteriologic advantages over bolus administration.[108] A recent Swedish study suggested that the outcome of longer 8-hour interval dosing compared with the recommended 6-hour interval dosing for β-lactams (other than ceftriaxone) might also be sufficient.[109] However, further studies are needed to identify optimal dosing duration and interval.

2.1.4 Choice of Empiric Therapy

Choice of empiric antibiotic therapy should be based on the most likely causative organism for the age of the patient.[89,92] However, choice of antimicrobial therapy must also take into account host factors, such as vaccination status, immune competence, and local antibiotic resistance patterns. Pre-hospital antibiotics are encouraged in meningococcal disease to improve the outcome.[92]

Most authorities in developed countries now recommend a third-generation cephalosporin, such as ceftriaxone or cefotaxime, as first-line, empiric therapy for ABM.[89,92,94] These agents have activity against all common meningeal pathogens (except *L. monocytogenes*), although there is increasing emergence of cephalosporin-resistant *S. pneumoniae* in some countries. In addition to excellent penetration into the CSF, these agents are easily administered one to three times daily. Infants under 3 months of age and adults over 50 years of age are more likely to have meningitis caused by *L. monocytogenes*; therefore, ampicillin should be added to this regimen.[89,94] Meningitis following trauma or neurosurgery carries a greater risk of infection with nosocomial and Gram-negative organisms. Broad-spectrum antibiotic therapy to cover these pathogens (such as vancomycin and ceftazidime) should be considered.[89]

For immunosuppressed individuals, the spectrum of likely causative organisms is much wider; therefore, antibiotics with a broader coverage should be used (table II).[89]

2.1.5 Antimicrobial Resistance

There are growing concerns regarding antimicrobial resistance in organisms causing ABM. Antimicrobial treatment must be adjusted to microbiology results so as to provide highly effective and narrowly focused bactericidal treatment.[104]

Streptococcus Pneumoniae (Pneumococci)

Antibiotic resistance is an increasing problem in *S. pneumoniae* infections. Penicillin-resistant pneumococci have been reported since 1967[110] and resistant strains have spread worldwide. Since the early 1980s, penicillin-resistant isolates have been reported from certain parts of Europe and the Mediterranean.[111,112] Sixteen resistant clones have contributed to the rapid increase in resistant pneumococcal strains worldwide.[113]

Table II. Empiric choice of antibiotic for meningitis according to age and underlying condition

Age	Empiric choice of antibiotic (intravenous)
0–3 mo[a,b]	*Broad spectrum cephalosporin and ampicillin*
	Cefotaxime 100 mg/kg 8-hourly
	Ceftriaxone 80 mg/kg 12-hourly
	Ampicillin 100 mg/kg 8-hourly
>3 mo–50 y[b]	*Broad spectrum cephalosporin*
	Cefotaxime 100 mg/kg 8-hourly (adult 2 g 8-hourly)
	Ceftriaxone 80 mg/kg 12-hourly (adult 2 g 12-hourly)
>50 y[b]	*Broad spectrum cephalosporin and ampicillin*
	Cefotaxime 100 mg/kg 8-hourly (adult 2 g 8-hourly)
	Ceftriaxone 80 mg/kg 12-hourly (adult 2 g 12-hourly)
	Ampicillin 100 mg/kg 8-hourly (adult 2 g 4-hourly)
Immunocompromised host	*Ceftazidime and ampicillin*
	Ceftazidime 50 mg/kg 8-hourly (adult 2 g 8-hourly)
	Ampicillin 100 mg/kg 8-hourly (adult 2 g 4-hourly)
Post-neurosurgery, post-skull trauma, cerebrospinal fluid shunt	*Ceftazidime and vancomycin*
	Ceftazidime 50 mg/kg 8-hourly (adult 2 g 8-hourly)
	Vancomycin 15 mg/kg 6-hourly (adult 2 g/24 hours)

a   In neonates, in particular preterm neonates, drug dosages may have to be adjusted.

b   Vancomycin 15 mg/kg 6-hourly (max. 2 g/24 hours, for resistant *Streptococcus pneumoniae*).

max. = maximum.

Resistance to penicillin and other antibiotics has been defined by the Clinical and Laboratory Standards Institute, Wayne, PA, USA.[114] Intermediate penicillin resistance is defined as an MIC of 0.1–1 μg/mL and high penicillin resistance as an MIC of ≥2 μg/mL. Highly-resistant strains are more likely to also be resistant to other β-lactam and non β-lactam antibiotics. The proportion of pneumococci resistant to penicillin has been reported to be 59% in Hungary,[115] 55% in children in Spain,[116] 25% in Atlanta, GA, USA[117] and only 3.6% in the UK.[118] In 1999 in Spain, 38% of all CSF isolates of pneumococcal meningitis were penicillin resistant.[119] More worrying perhaps is the emergence of cephalosporin-resistant strains.[120] In Spain, 6% of pneumococci causing pneumonia in 1994 were cephalosporin resistant (MIC 1–4 μg/mL) but were not asso-

ciated with excess mortality or morbidity following treatment with these antibiotics,[121] a finding echoed by Tan et al.[122] in 1998. In pneumococcal meningitis, strains are considered to have resistance to cefotaxime and ceftriaxone if the MIC is ≥0.5 μg/mL, and to be highly resistant if the MIC is ≥2.0 μg/mL.[114] There are a number of reports of treatment failures with third-generation cephalosporins;[120,123,124] however, there is some evidence that the outcome is not altered when antibiotics with an MIC = 1.0 μg/mL are used for treatment.[124] The risk of colonization with penicillin-resistant pneumococci increases with previous antibiotic use, in children aged <5 years, and with daycare attendance.

Vancomycin resistance to pneumococci has not yet been reported as a significant clinical problem, and combination therapy with vancomycin and a cephalosporin is now recommended for children in the US when pneumococcal meningitis is suspected.[89] In pneumococcal meningitis, vancomycin (at a dosage of 60 mg/kg/day) in combination with dexamethasone achieves good penetration across the CSF,[125] and there is evidence of synergism when vancomycin is combined with ceftriaxone or cefotaxime.[126] However, there are some reports of vancomycin-tolerant pneumococcal strains associated with meningitis,[127] and of treatment failures in adults that were associated with poor CSF penetration of vancomycin at a dosage of 30 mg/kg/day.[128] There is experimental evidence of delayed sterilization of CSF in animal models when vancomycin is administered with dexamethasone,[129] and there are concerns about the potential effect of this finding on clinical outcome in adult patients.[130] Considering the growing impact of resistant pneumococci, the NICE in the UK has recommended vancomycin to be added to the third-generation cephalosporin in suspected bacterial meningitis if the patient has travelled outside of the UK or has had prolonged or multiple exposure to antibiotics in the past 3 months.[92] However, this has been questioned by some experts in view of the negligible incidence of cephalosporin-resistant pneumococci in the UK.[131]

Rifampin penetrates the CSF well,[125] is unaffected by concomitant dexamethasone administration,[129] and has been used successfully in combination with other antibiotics in the treatment of cephalosporin-resistant pneumococcal meningitis.[132] It is recommended in pediatric practice when the combination of vancomycin and cephalosporin is failing.[89]

Another group of antibiotics against which pneumococcal resistance is seen are the macrolides. Macrolide resistance is especially common in Mediterranean countries, where it is reported in up to 20% of pneumococcal isolates.[32,133] The prevalence of quinolone-resistant pneumococci is low, despite some reports of resistant strains from Spain and Greece.[32] The

resistance pattern also reflects the pattern of antibiotic usage, varies among different regions and countries, and evolves over time. Surveillance studies showed an incidence of multidrug-resistant (resistant to at least three antibiotics) pneumococci of 9–24% in the US in 1994–2007,[32] 15.8% in Europe in 2004–5 (varying between 0% and 42.9% in different countries),[134] and 26.8% in Asia in 2000–1, with extremely high incidences in Vietnam (71.4%) and Korea (45.2%).[135] Whether antimicrobial resistance impacts on clinical outcome is controversial in these areas.[32]

Neisseria Meningitidis (Meningococci)

Penicillin resistance to *N. meningitidis* has been reported in a number of countries.[104,134-139] Up to 71.4% of *N. meningitidis* isolates in Spain in 1997 were resistant to penicillin, and most of the resistance was related to changes in the penA gene, which codes for penicillin-binding protein 2 (PBP2).[140] Despite these reports, treatment with penicillin has been generally effective globally in treating *N. meningitidis* meningitis.[140] However, a recent report from Spain indicates that treatment of resistant strains with penicillin is associated with a poorer outcome, and that the use of a third-generation cephalosporin is recommended for the treatment of *meningococcal* meningitis in these areas.[139]

In the meningitis belt of Africa, the WHO recommends use of a single 100 mg/kg dose of oily chloramphenicol for the treatment of *meningococcal* meningitis in patients above 2 years of age, an effective dosage during epidemics.[141] There is little reported resistance against chloramphenicol, and the drug is also effective against pneumococci and haemophilus.[142] The third-generation cephalosporins, and vancomycin, are prohibitively expensive in these resource-poor countries, and regular use of rifampin is avoided because of the fear of an increase in resistant tuberculosis. Therefore, despite the increased side effects of chloramphenicol, it remains the drug of choice for the treatment of *meningococcal* meningitis in these regions.[142]

There is an emphasis on developing cheaper third-generation cephalosporins for use in the developing world, and ceftriaxone is being recommended as a single-dose treatment for meningococcal meningitis during epidemics.[141] In developed countries, third-generation cephalosporins are used as first-line therapy for the treatment of meningococcal meningitis; no resistance has been reported against these drugs.

Urgent chemoprophylaxis is indicated to eradicate nasopharyngeal colonization of *N. meningitidis* in close contacts of the index case, and this usually reduces nasopharyngeal carriage by 90%.[143] Rifampin and ciprofloxacin are commonly used for prophylaxis, but some resistance to rifampin has been reported in Germany, the US, and Italy.[144-146] However,

ciprofloxacin as a single dose works well in clearing the bacteria from the nasopharynx. Resistance of *N. meningitidis* to fluoroquinolones is rarely reported, and only at a low level (MIC 0.12–0.25 mg/L); to date, one strain has been reported in Greece[147] and a few strains in England, Wales,[148] and Spain.[149]

Haemophilus Influenzae

Ampicillins were commonly used to treat Haemophilus infections, until resistance emerged in the 1980s.[150] β-Lactamase-producing strains of Hib accounted for 32% of all isolates in the US,[7] and, in parts of Nigeria, up to 15% of Hib isolates are chloramphenicol resistant.[151] In countries that have not adopted the Hib conjugate vaccine, meningitis due to penicillin- and chloramphenicol-resistant strains is a continuing clinical problem.[152] The third-generation cephalosporins, cefotaxime and ceftriaxone are effective in the treatment of chloramphenicol-resistant strains of Hib. Chemoprophylaxis with rifampin can be used with high efficacy to prevent secondary cases in close contacts of an index case with Hib disease.[143]

2.1.6 Evaluation of Newer Antibiotics

Cautious and selective use of available antibiotics titrated to microbial sensitivities is very important in preventing the spread of multiresistant bacteria. Because of increasing reports of resistant bacteria causing ABM, some exploration of other antibiotics active against the three commonly incriminated bacteria is warranted.

Meropenem has good CSF penetration and a broad spectrum of activity against Gram-positive and Gram-negative bacteria, including many of those that produce β-lactamases.[153,154] Animal and human studies have shown the efficacy of meropenem in penicillin- and cephalosporin-susceptible and resistant pneumococcal meningitis.[155,156] Faropenem is another derivative of the same group and shows low MICs (≤1 μg/L) to both penicillin susceptible and non-susceptible pneumococci.[157]

Cefepime, one of the fourth-generation cephalosporins, showed superior CSF pharmacodynamics against pneumococci compared with ceftriaxone in one recent study.[158] Fluoroquinolones have been used successfully in some patients with Gram-negative meningitis.[89]

Some of the quinolone derivatives, such as gatifloxacin, garenoxacin, and moxifloxacin, have shown good penetration in inflamed meninges;[159-162] they are lipophilic in nature and can achieve peak concentrations rapidly with an extended half-life.[102] Ciprofloxacin has been used in the treatment of Gram-negative ABM.[89] However, fluoroquinolones should only be used in multidrug-resistant meningitis or where standard therapy

has failed, because the efficacy of fluoroquinolones as monotherapy has not been established in penicillin-resistant pneumococci and there are only limited data in children and neonates.

The combination of ceftriaxone with rifampin has been shown to be as efficacious as a combination of ceftriaxone with vancomycin in treating pneumococcal meningitis in a rabbit model.[163] Linezolid is another antibiotic that has been suggested as an alternative to vancomycin and rifampin in combination with ceftriaxone for use against penicillin-resistant pneumococcal strains.[164] There has been some interest in other drugs, such as quinupristin/dalfopristin, in treating multidrug-resistant pneumococci.[153] Daptomycin, a lipopeptide with excellent action against a variety of Gram-positive bacteria, acts by disrupting several aspects of bacterial cell membrane function and shows high bactericidal activity in animal models of ABM;[165] it has primarily been used in adults with skin and soft-tissue infections.

2.2 Inflammation in Meningitis

Despite effective antimicrobial therapy, neurologic morbidity and mortality remains a major problem in ABM. Brain inflammation and edema is mediated by the activation of host inflammatory pathways by bacterial products, such as endotoxin and peptidoglycans.[166] This results in the release of a number of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, which in turn stimulate the inflammatory cascade, releasing platelet-activating factor, IL-8, and interferon-γ.[167-169] The resulting upregulation of cellular-adhesion molecules of the vascular endothelium and blood leukocytes, and the release of toxic products from activated neutrophils, mediate meningeal inflammation, disruption of the BBB, microvascular thrombosis, and vasogenic and cytotoxic cerebral edema.[167,169]

2.2.1 Anti-Inflammatory Treatment

This evidence has led to the hypothesis that brain injury may be reduced by the use of anti-inflammatory therapy.[170] Adjunctive corticosteroid therapy was found to be effective in experimental animal models,[169] and, in these models, a number of other immunomodulatory agents have been shown to successfully reduce inflammation. These immunomodulatory agents include polymyxin B, which neutralizes endotoxin;[159] antibodies directed against TNF-α and IL-1β;[169,170] agents that block endotoxin binding to macrophages (e.g. bactericidal/permeability increasing protein (BPI) l and anti-CD14 antibodies);[171,172] and antibodies directed against neutrophil-

adhesion molecules.[173] BPI proved safe and successful in reducing morbidity from meningococcal septicemia on subgroup analysis in a multicenter, randomized, placebo-controlled trial in children, but has not yet been used specifically in ABM.[174]

Adjunctive Corticosteroids

The role of adjunctive corticosteroids in ABM has been widely studied in the last three decades. Initial trials showed a clear benefit from dexamethasone, with a decrease in neurologic sequelae, particularly nerve deafness.[175] Subsequent studies from other countries also reported a reduction in neurologic sequelae following the use of dexamethasone;[176,177] however, there were some problems with applying the results of these trials widely. The majority of patients in these early studies were infected with Hib, and studies specifically addressing pneumococcal meningitis in children, although demonstrating an improved neurologic outcome, did not reach statistical significance.[178]

One of the few properly conducted studies of the use of dexamethasone in adults with meningitis recently reported a trend toward improved outcome in the dexamethasone group compared with the non-dexamethasone group (74% vs 52% with no neurologic sequelae), but this was not statistically significant.[179] The trial only included patients with pneumococcal and meningococcal meningitis and was stopped prematurely because of a change in antibiotic recommendations. Dexamethasone was administered up to 3 hours post-antibiotic, which may have reduced its effectiveness. Another study in adults demonstrated a benefit only in pneumococcal meningitis; however, this was not a placebo-controlled or double-blinded study.[177] In 2007, a Cochrane analysis published a review of 20 randomized clinical trials on the safety and efficacy of corticosteroid use in ABM.[180] According to this analysis, adjuvant corticosteroids were associated with lower case fatality rates (relative risk [RR] 0.83; 95% CI 0.71, 0.99), lower rates of severe hearing loss (RR 0.65; 95% CI 0.71, 0.99), and fewer long-term neurologic sequelae (RR 0.67; 95% CI 0.45, 1.00).[180] In children, the beneficial effects of corticosteroid use were less convincing, although there was a trend towards reduced hearing loss and short-term neurologic sequelae in non-Hib meningitis, with the effect statistically significant in high-income countries compared with low-income countries. Subgroup analysis suggested that the case fatality rate was reduced by adjuvant steroids in patients with pneumococcal meningitis (RR 0.59; 95% CI 0.45, 0.77) and that hearing loss was reduced in patients with Hib meningitis.[180] A more recent meta-analysis by the same group showed no significant reduction in death and neurologic disability with corticosteroid use in any of the prespecified age groups.[181]

There are theoretical disadvantages to the use of cortico-steroids, such as the reduction of vancomycin penetration into the CSF in animal models of pneumococcal meningitis (a finding not confirmed in children),[125] the possibility of neuronal injury,[94] and the down-regulation of potentially beneficial anti-inflammatory cytokines, such as IL-10.[182] However, a recent trial in adults did not substantiate the effect of dexamethasone on reducing vancomycin levels in the CSF.[182]

Despite a lack of robust evidence for the beneficial effects of routine dexamethasone use in children with ABM from various meta-analyses, subgroup analyses have suggested that it may have a beneficial role in high-income countries. In the absence of any potentially significant harmful effects, dexamethasone is recommended for use in children with ABM above 3 months of age in the UK[92] and above 6 months of age in the US.[183] The recommended dosage is 0.6 mg/kg/day in four divided doses for 4 days prior to or simultaneously with the first dose of anti-biotic, or within 4 hours of antibiotic administration.[92] In adults, the evidence is less convincing. However, in severe ABM, there are theoretical grounds for using steroids at the same recommended dosage as above; there is little evidence of a worse outcome.[184] There is no good evidence to date to recommend the routine use of steroids for ABM in neonatal meningitis or post-neurosurgical patients.

Other Adjuvant Anti-Inflammatory Therapies

There are no reported clinical studies of the use of other anti-inflammatory therapies in the treatment of ABM. However, there are several potential target therapies, which are in the experimentation phase at present. These include neutralization of bacterial factors that induce host inflammatory cytokines, modulation of host inflammatory cytokines, and neutralization of consequences of injury.[142] There is some evidence for the use of glycerol as a hyperosmolar agent to reduce neurologic sequelae.[185] However, more recent evaluation from the same study group did not show a role for either dexamethasone or glycerol in reducing hearing loss when used to treat ABM.[186]

3. Antibiotic Recommendations

The recommended antibiotics and dosages for the treatment of ABM caused by specific organisms are outlined in table III.

3.1 Duration of Therapy

The duration of antibiotic treatment for meningitis is not generally based on evidence from clinical trials, but more on

Table III. Recommended antibiotic therapy for specific pathogens

Organism	Antibiotic (intravenous)
Neisseria meningitidis	*Broad spectrum cephalosporin*
	Cefotaxime 100 mg/kg 8-hourly (adult 2 g 8-hourly)
	Ceftriaxone 80 mg/kg 12-hourly (adult 2 g 12-hourly)
	Benzylpenicillin (depending on sensitivities)
	300 000 units/kg/day (max. 24 million units/ 24 hours)
Streptococcus pneumoniae	*Broad spectrum cephalosporin and vancomycin*
	Cefotaxime 100 mg/kg 8-hourly (adult 2 g 8-hourly)
	Ceftriaxone 80 mg/kg 12-hourly (adult 2 g 12-hourly)
	Vancomycin 15 mg/kg 6-hourly (max. 2 g/ 24 hours)
Hemophilus influenzae	*Broad spectrum cephalosporin*
	Cefotaxime 100 mg/kg 8-hourly (adult 2 g 8-hourly)
	Ceftriaxone 80 mg/kg 12-hourly (adult 2 g 12-hourly)
Listeria monocytogenes	*Ampicillin and gentamicin (synergistic activity)*
	Ampicillin 100 mg/kg 8-hourly (adult 2 g 4-hourly)
	Gentamicin 2.5 mg/kg 8-hourly
Staphylococcus agalactiae	*Ampicillin and gentamicin (synergistic activity)*
	Ampicillin 100 mg/kg 8-hourly (adult 2 g 4-hourly)
	Gentamicin 2.5 mg/kg 8-hourly

max. = maximum.

historic practice, although there have been some studies investigating courses of therapy that are shorter than traditionally recommended. A recent meta-analysis of the duration of antibiotic therapy in children, and its impact on outcome, has not shown any conclusive evidence to support long or short courses of antibiotics, and the authors emphasized the lack of evidence in the field.[187] For pneumococcal meningitis, 14 days of therapy is recommended; group B streptococcal or *L. monocytogenes* meningitis should be treated for 14–21 days, and Gram-negative infections should be treated with at least 21 days of antibiotics.[187] Clinical trials have confirmed that antibiotic therapy with ceftriaxone, cefotaxime, chloramphenicol, or penicillin for 7 days was very effective for meningococcal meningitis, and that many patients were cured within 5 days.[188,189] *H. influenzae* meningitis can also be treated effectively with a 7-day course of antibiotics.[189] However, these recommendations should be reviewed in light

of the clinical and microbiologic response to therapy, and may need to be adapted for the individual patient, especially if there are complications or if the individual is immunocompromised.

4. Conclusions

Despite effective antibiotic therapy, the treatment of ABM remains a controversial topic. The morbidity and mortality are significant and the use of adjuvant corticosteroids continues to be debated in pediatric and adult practice. Newer anti-inflammatory treatments are likely to be beneficial in reducing neurologic morbidity, but have not yet been studied in clinical trials. Antibiotic resistance is evolving and becoming a global issue requiring continued surveillance of clinical isolates and frequent review of therapy recommendations to take into account the emerging resistance patterns of ABM-causing organisms. The virtual eradication of Hib meningitis in countries that have adopted routine immunization with conjugate Hib vaccine shows how vaccination can change the epidemiology of disease in a short time. Effective vaccines against *S. pneumoniae* and *N. meningitidis* may reduce the burden of disease caused by these pathogens in the future.

Acknowledgments

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