

Bacterial Meningitis in Children

Critical Review of Current Concepts

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Contents

Abstract	1097
1. Aetiological Agents	1098
2. Principles of Antibacterial Therapy	1099
3. Antibacterial Agents	1100
3.1 <i>Streptococcus pneumoniae</i>	1100
3.2 <i>Haemophilus influenzae</i> Type B	1104
3.3 <i>Neisseria meningitidis</i>	1104
4. Adjunctive Dexamethasone Therapy	1104
5. Other Adjunctive Anti-inflammatory Agents	1106
6. Other Considerations	1107
6.1 Syndrome of Inappropriate Antidiuretic Hormone Secretion	1107
6.2 Prophylaxis	1107
6.3 Vaccination	1108
7. Conclusions	1109

Abstract

Acute bacterial meningitis is still an important cause of morbidity and mortality in children worldwide. Recently, *Haemophilus influenzae* type b (Hib), once a common cause of meningitis, has virtually disappeared in developed nations, reflecting the overwhelming success of Hib vaccination. Unfortunately, Hib remains a significant pathogen in resource-poor countries. The introduction of the conjugated pneumococcal vaccine in 2000 may lead to similar future trends as witnessed with Hib. As the resistance of *Streptococcus pneumoniae* to penicillin and cephalosporins continues to evolve, vancomycin has become an important antibacterial in the treatment of bacterial meningitis. The unreliable penetration of this agent into cerebrospinal fluid is of concern, which is compounded by the controversial use of corticosteroids in paediatric meningitis. Some data suggest that in certain situations the addition of rifampicin (rifampin) to ceftriaxone may be a better choice. While dexamethasone is now considered the standard adjunctive therapy in the treatment of pneumococcal meningitis in adult patients, the benefit in children is not so clear and remains controversial; thus, there is no definitive paediatric recommendation. Several anti-inflammatory agents currently under investigation may be used in the future as adjunctive therapy for bacterial meningitis.

It is clear that the current concepts in the treatment of childhood bacterial meningitis are evolving, and other antibacterial options and possible alternatives such as carbapenems and fluoroquinolones should be considered. Fluid restriction

because of the Syndrome of Inappropriate Antidiuretic Hormone Secretion is widely advocated and used. Yet, this practice was recently challenged. It seems that most patients with meningitis do not need fluid restriction. The overwhelming success of the conjugated Hib vaccine and the encouraging results of the new conjugated pneumococcal and meningococcal vaccines suggest that the ideal management of bacterial meningitis is prevention and vaccines development against the most common bacterial agents are the best solution.

Acute bacterial meningitis remains an important cause of high morbidity and mortality in the paediatric population worldwide. In developed countries over the past 2 decades, two major changes have occurred in the epidemiology of bacterial meningitis; both have significantly altered the management and empirical therapy of this disease (mostly in developed countries). First, *Haemophilus influenzae* type b (Hib), which once accounted for 70% of bacterial meningitis cases in children <5 years of age,^[1] has been virtually eradicated in those countries that introduced immunisation of infants with conjugate Hib vaccines. As a result, *Streptococcus pneumoniae* has become the most common pathogen beyond the neonatal period^[2] and the median age of patients with bacterial meningitis has increased from 15 months to 25 years with a predominance of adults rather than children. Unfortunately, in many resource-poor countries, where the Hib vaccine is not available, invasive Hib diseases (including meningitis) are still common and an estimated 350 000–700 000 children die from this infection every year.^[3] In addition, at least 1.2 million cases of meningococcal meningitis worldwide (with 10% mortality) occur each year (apart from epidemics that occur periodically in sub-Saharan Africa, the Middle East, India and China).

A second major epidemiological change is the emergence of penicillin and cephalosporin-resistant *S. pneumoniae*. In 1967, penicillin-resistant *S. pneumoniae* strains were first reported,^[4] and multi-drug resistance is now a worldwide phenomenon.^[5,6] As a result, a third-generation cephalosporin plus vancomycin has become the standard recommendation for empirical therapy for bacterial meningitis.^[7] As cephalosporin-resistant strains are re-

ported, the unreliable penetration of vancomycin into the CNS may become a major therapeutic issue.

During the era when Hib was a common cause of meningitis, the adjunctive use of dexamethasone was common practice when initiating therapy. Presently, the use of dexamethasone for meningitis caused by other bacteria is controversial rather than universally accepted. In a recent study of adult patients with meningitis, a significant decrease in mortality was associated with the concomitant use of dexamethasone.^[8] Should these results be considered when caring for the paediatric patient with meningitis? As the aetiological agents of bacterial meningitis and antibacterial resistance patterns change, it is certainly important to discuss modifications in the management of paediatric patients with this disease.

1. Aetiological Agents

This review focuses on bacterial meningitis in the otherwise healthy child beyond the neonatal and early infant period (age ≥ 3 months). In developed countries, the likelihood of Hib meningitis in a child who has received at least two doses of Hib vaccine is exceedingly rare. As a result of routine Hib vaccination, the incidence of invasive Hib disease in the US has declined by at least 97%, from 41 cases per 100 000 (1987) to 1.3 cases per 100 000 (1997).^[9] The decline in Hib disease has caused *S. pneumoniae* to become the most common aetiological agent of bacterial meningitis. In 1995, the US Centers for Disease Control and Prevention (CDC) performed a multistage surveillance study of bacterial meningitis and reported *S. pneumoniae* as the most commonly identified agent (47%), followed by *Neisseria meningitidis* (25%) and group B strepto-

cocci (12%).^[10] Hib remains a common pathogen in resource-poor nations where Hib vaccination is not readily available.

Although *S. pneumoniae* is currently the most commonly isolated agent, its epidemiology continues to evolve as a result of the introduction of the conjugate pneumococcal vaccine in early 2000. In the US, widespread use of this vaccine has already led to a reduction in the incidence of paediatric invasive pneumococcal disease; the CDC reported a 59% decline in the rate of pneumococcal meningitis from 1998 to end of 2001.^[11] The same results (66% reduction) were recently reported by Kaplan et al.^[12]

The peak incidence of meningococcal disease occurs in the first year of life, and 35–40% of cases occur in children <5 years of age.^[13,14] In The Netherlands, the case fatality rate during a meningococcal meningitis epidemic in 1989–90 was 4.6%.^[15] Recently, an increase in clusters of meningococcal disease due to *N. meningitidis* serogroup C was reported from various developed countries (e.g. Canada, the US, England, Spain). The use of conjugate meningococcal C vaccine has been effective in terminating the spread of this infection. For example, an overall reduction of 86.7% in the incidence of serogroup C infection occurred in the UK from 1999 to 2001, with a concomitant decrease in deaths, from 67 in 1999 to 5 in 2001.^[16] In sub-Saharan Africa, *N. meningitidis* remains the most frequently isolated organism, accounting for up to 61% of cases.^[17] Cyclical epidemics of meningococcal meningitis, which occur every 5–10 years during the dry months, may result in >300 000 cases (with 10% mortality).^[18] Serogroup A has been the most common cause of epidemic and endemic meningococcal disease; however, a shift to serogroup W135 has occurred recently during the Hajj (pilgrimage) season.

2. Principles of Antibacterial Therapy

The cerebrospinal fluid (CSF) has poor ability to respond to bacterial infection. It is a fluid with inadequate immunoglobulin and complement activity, resulting in impaired ability to opsonise and phagocytise infecting organisms. Thus, sterilisation

of the CSF, or bacteriological cure, depends on the antibacterial agent(s) used. Several factors are important for the rapid CSF sterilisation which is required for optimal therapy. For β -lactam therapy, there is a significant correlation between increasing drug concentration in the CSF and increasing bactericidal rates. Maximal bactericidal activity occurs when the CSF concentration is 10–30 times higher than the *in vitro* broth minimal bactericidal concentration (MBC).^[19] The aminoglycosides and fluoroquinolones also exhibit an excellent correlation between the CSF concentrations and the bactericidal activity (i.e. the higher the concentration, the better the bacterial killing).^[20–22] The maximum bactericidal activity of vancomycin occurred when the CSF concentrations were five to ten times higher than the MBC.^[23] In contrast, increasing the CSF concentrations of rifampicin (rifampin) were not associated with increased killing rate.^[24]

The CSF penetration of an antibacterial depends on the integrity of the blood-brain barrier (BBB) and the physical and chemical characteristics of the drug. For example, β -lactam antibacterials penetrate poorly in the setting of a normal BBB (approximately 0.5–2.0% of peak serum concentrations). However, in the setting of meningitis, β -lactam penetration across the BBB is significantly enhanced (up to 55% of the peak serum concentration). As demonstrated in the rat meningitis model, the improved penetration results from separation of the intercellular tight junctions and increased vesicular transport.^[25] To ensure optimal penetration of the antibacterial into the CNS, maximal parenteral dose administration should be maintained for the entire treatment course; as meningeal inflammation decreases with therapy, antibacterial penetration across the BBB diminishes (e.g. CSF penicillin concentrations were reduced by almost 50% on day 5 of therapy compared with day 1^[26]). Certain characteristics of the antibacterial agent itself may also alter its ability to penetrate the BBB. Factors that improve the ability of a drug to cross the BBB include a low molecular weight, simple chemical structure, high lipid solubility, low degree of protein binding and low degree of ionisation.^[27] Of note, vancomycin can penetrate the CSF

only if the BBB has been damaged significantly, which may explain the wide range of CSF concentrations during meningitis.^[28]

In the setting of purulent meningitis, the antibacterials used have varying bactericidal effects. The protein-rich environment of purulent meningitis may decrease the activity of β -lactams. These antibacterials are highly protein-bound, but it is the free (unbound) drug that is needed for a bactericidal effect. The decreased pH in CSF during purulent meningitis may alter the activity of certain classes of antibacterials, such as the aminoglycosides. In addition, the elimination of some drugs from the CSF (e.g. penicillin) is slowed by the inflammatory response, allowing higher concentrations in the CSF.^[29]

An understanding of the pharmacodynamic characteristics of a therapeutic agent in the CSF is also important when choosing appropriate dose administration regimens. Antibacterial activity can display two patterns of killing, either concentration- or time-dependent. In concentration-dependent killing, the drug displays bacterial killing over a wide range of antibacterial concentrations that exceed the minimum inhibitory concentration (MIC). There is a direct correlation between the achieved drug concentrations and the rate of bacterial killing. This pattern is seen with the aminoglycosides and fluoroquinolones, where increasing CSF concentrations resulted in higher rates of bacterial killing which allows for less frequent dose administration.^[30]

The second pattern of killing is time-dependent killing. For these antibacterials, the most important factor for bactericidal activity is the length of time that the CSF concentration is higher than the MIC and/or the MBC. The time above the MBC correlates better with efficacy. With these agents (e.g. vancomycin and the β -lactams), bactericidal activity is reached by giving the drug at frequent intervals, in order to keep the concentration of the drug above the MIC for the longest time period possible.^[30]

It is generally believed that even a short delay in initiation of antibacterial therapy for bacterial meningitis will have a deleterious effect on the outcome. Yet, most studies that examined the impact of the

timing of antibacterial administration upon clinical outcome could not find a correlation between the duration of symptoms before antibacterials were initiated and the clinical outcome. Aronin et al.^[31] studied a prognostic model for 269 adults with bacterial meningitis and showed that the impact on clinical outcome varied with the initial severity of illness at presentation and not with a specific time delay in the administration of the first dose of antibacterial.^[31] Hypotension, altered mental status and seizures at presentation were associated with poorer outcome. Thus, a delay in treatment (even up to 72–96 hours), when a patient has presented with a nonspecific illness, will not alter the risk of sequelae.^[32] In patients with overt symptoms of meningitis, a delay in starting therapy may increase the risk of sequelae, depending on the combinations of presenting symptoms mentioned earlier.

3. Antibacterial Agents

Empirical therapy of a child with suspected bacterial meningitis is based on the most likely pathogens for the patient's age and susceptibility patterns in that geographical location. Once the organism is identified and its antibacterial susceptibilities determined, therapy should be modified as needed.

3.1 *Streptococcus pneumoniae*

The recommendations for antibacterial therapy for pneumococcal meningitis are based on current *in vitro* susceptibility patterns (table I). Currently, in some geographical areas of the US >40% of pneumococcal isolates from sterile body sites (not exclu-

Table I. National Committee for Clinical Laboratory Standards minimal inhibitory concentration breakpoints for antibacterial agents used to treat *Streptococcus pneumoniae* infections^[37]

Antibacterial agent	Susceptible ($\mu\text{g/mL}$)	Nonsusceptible ($\mu\text{g/mL}$)	
		intermediate	resistant
Penicillin	≤ 0.06	0.1–1.0	≥ 2.0
Ceftriaxone	≤ 0.5	1.0	≥ 2.0
Cefotaxime	≤ 0.5	1.0	≥ 2.0
Vancomycin	≤ 1.0		
Rifampicin	≤ 1.0	2.0	≥ 4.0
Chloramphenicol	≤ 4.0		≥ 8.0
Meropenem	≤ 0.12	≥ 0.25	

Table II. Antibacterial therapy suggestions for children with bacterial meningitis

Organism	Antibacterial of choice	Alternatives
<i>Neisseria meningitidis</i>		
Sensitivity unknown	Ceftriaxone or cefotaxime	Chloramphenicol
Penicillin susceptible	Penicillin or ceftriaxone or cefotaxime	Ampicillin or chloramphenicol
Penicillin resistant	Ceftriaxone or cefotaxime	Chloramphenicol
β-Lactam allergy	Chloramphenicol	
<i>Haemophilus influenzae</i>		
Sensitivity unknown	Cefotaxime or ceftriaxone or ampicillin plus chloramphenicol	
Ampicillin susceptible	Ampicillin or cefotaxime or ceftriaxone	Chloramphenicol
Ampicillin resistant	Cefotaxime or ceftriaxone	Chloramphenicol
β-Lactam allergy	Chloramphenicol	
<i>Streptococcus pneumoniae</i>		
Sensitivity unknown	Cefotaxime or ceftriaxone plus vancomycin	Chloramphenicol
Penicillin susceptible	Penicillin or cefotaxime or ceftriaxone	Ampicillin or chloramphenicol
Penicillin intermediate or resistant	Cefotaxime or ceftriaxone	Chloramphenicol
Cephalosporin nonsusceptible	Cefotaxime or ceftriaxone plus vancomycin ^a Cefotaxime or ceftriaxone plus rifampicin (rifampin) ^{a,b}	Chloramphenicol or meropenem
β-Lactam allergy	Vancomycin plus rifampicin	Meropenem

a Do not use as monotherapy.

b Only if minimal bactericidal concentration $\leq 4 \mu\text{g/mL}$.

sively CSF) are nonsusceptible to benzylpenicillin (penicillin G) and up to 50% of these isolates are highly resistant. Approximately half of these penicillin-nonsusceptible strains are also nonsusceptible to both ceftriaxone and cefotaxime.^[33] Although CSF isolates are somewhat less resistant to these antibacterials, the percentage is still high. For example, in a recent multicentre surveillance of only CSF isolates, approximately 20% were penicillin nonsusceptible and 7% were ceftriaxone nonsusceptible.^[34] Resistance to penicillin and third-generation cephalosporins has also been reported worldwide. Thus, the American Academy of Pediatrics (AAP) currently recommends empirical combination therapy with vancomycin and cefotaxime or ceftriaxone.^[33] It was suggested that this combination is synergistic in experimental pneumococcal meningitis^[35] and in children (table II).^[36]

At present, pneumococcal resistance to vancomycin has not been reported; however, treatment failure with vancomycin (both as monotherapy and combination therapy) has been reported. Monotherapy with vancomycin is not recommended, as CSF penetration is inconsistent and bactericidal concen-

trations may not be sustained, especially in the setting of less inflamed meninges. In a study of 11 adults with pneumococcal meningitis, four patients had clinical failure with vancomycin monotherapy.^[38] In two of these patients, CSF drug concentrations were undetectable at 48 hours after onset of therapy. Concomitant use of dexamethasone and variability in serum concentrations were thought to be a possible contributors to these failures. Although the combination of vancomycin with a third-generation cephalosporin seems to be effective, careful monitoring of patients receiving this combination is needed. While limited data suggest that CSF vancomycin concentrations exceed the MBC_{90} for *S. pneumoniae* (2- to 6-fold),^[36] these concentrations are not consistently 5- to 10-fold higher, which is the concentration needed for maximal bactericidal killing. There is evidence that delayed sterilisation of the CSF can contribute to a worse outcome.^[39] The wide variation in vancomycin penetration into the CSF may result in lower drug concentrations and slower sterilisation that will affect the clinical outcome. This effect may be exaggerated when vancomycin is given with dexamethasone.^[40] It is possible

that with the increase in *S. pneumoniae* resistance to third-generation cephalosporins, the 'protective effect' of these agents against vancomycin failures as a result of poor CSF penetration will be diminished and treatment failures with the combination will occur.

While pneumococcal resistance to vancomycin has not been reported, the development of drug tolerance (i.e. the organism is unable to replicate but is not killed) was recently observed. In 1999, a cephalosporin- and vancomycin-tolerant strain of *S. pneumoniae* was isolated from the CSF of a patient whose symptoms recurred while receiving therapy with vancomycin and a third-generation cephalosporin.^[41] The isolate was also tolerant to aminoglycosides and fluoroquinolones. The sensitivity to rifampicin was not reported. Thus, if a patient with bacterial meningitis demonstrates clinical failure, a poor response to therapy or disease recurrence once therapy is discontinued, clinicians should have a high index of suspicion for vancomycin failure due to poor penetration or to a tolerant strain. It should be noted that no additional cephalosporin- and vancomycin-tolerant pneumococcus strain has been isolated to date.

The addition of rifampicin to ceftriaxone has been demonstrated to result in significantly enhanced CSF bactericidal activity compared with that of ceftriaxone alone against cephalosporin-resistant strains.^[36] In addition, this combination reduced mortality by almost 50% in the animal meningitis model,^[42] probably by decreasing the release of teichoic and lipoteichoic acids from pneumococci, which modulated the magnitude of the inflammatory response.^[43] Other data show that the CSF penetration of rifampicin is excellent and is unaffected by the concomitant use of dexamethasone. For these reasons, rifampicin instead of vancomycin as adjunct to a third-generation cephalosporin is recommended by some investigators, especially if dexamethasone is used (table II). Rifampicin should never be used alone for treatment, as resistance will develop rapidly. In addition, although limited data suggest that rifampicin maybe synergistic with ceftriaxone against cephalosporin-resistant *S. pneumo-*

niae, caution should be taken in using this combination if the isolated strain is highly resistant to cephalosporins. Additional trials are needed to investigate whether the beneficial effect of rifampicin shown in the animal model of pneumococcal meningitis makes it the preferred drug over vancomycin. Many other features of rifampicin suggest that it may be a better choice.

As penicillin and cephalosporin resistance continues to emerge, other antibacterials have been evaluated as alternative options, including the carbapenems. Imipenem/cilastatin is associated with a high incidence of drug-related seizure activity; thus, its usefulness is limited in the treatment of CNS infections. However, meropenem is considered to be an alternative therapeutic agent for bacterial meningitis in children ≥ 3 months of age. In a study comparing the efficacy and safety of meropenem to that of cefotaxime, no significant difference in clinical outcome was found between the two treatment groups. Clinical cure with or without sequelae was reached in 97% and 96% of the meropenem- and cefotaxime-treated patients, respectively.^[44] At the 5- to 7-week follow-up, 54% of the meropenem- and 58% of the cefotaxime-treated patients were without neurological sequelae.

Cefuroxime, a second-generation cephalosporin, is not recommended for the treatment of pneumococcal meningitis. It became less favoured for the empirical treatment of bacterial meningitis when clinical trials demonstrated superior results with third-generation cephalosporins in the treatment of meningitis. Ceftriaxone (compared with cefuroxime) was shown to sterilise CSF faster (2% vs 12% CSF cultures positive at 18–36 hours) and resulted in a lower incidence of hearing loss (4% vs 17%).^[39] However, it is important to note that all patients with delayed CSF sterilisation had Hib infection. In addition, of the 11 patients who developed hearing impairment, 8 (73%) had Hib meningitis, 2 (18%) had *S. pneumoniae* and 1 (9%) had *N. meningitidis* infection.

The new fluoroquinolones are more effective than cephalosporins *in vitro* against pneumococci and *H. influenzae*.^[45] An *in vitro* comparison of the

activity of moxifloxacin, penicillin, ceftriaxone and ciprofloxacin against *S. pneumoniae* demonstrated that moxifloxacin was 32-fold more active than ciprofloxacin and was not affected by penicillin and cephalosporin resistance.^[46] In a rabbit meningitis model, gemifloxacin reduced bacterial titres in CSF almost as rapidly as ceftriaxone; coadministration of dexamethasone did not affect gemifloxacin serum or CSF concentrations.^[47] In another rabbit model, gatifloxacin was found to have excellent CNS penetration and was effective monotherapy against cephalosporin-resistant pneumococci.^[48] Successful treatment with ciprofloxacin and pefloxacin of nosocomial meningitis in adults and newborns has been reported.^[49] Thus, although not standard therapy, the fluoroquinolones have been investigated for use in CNS infections. Trovafloxacin was found to be as effective as ceftriaxone in a large paediatric study;^[50] however, concerns regarding trovafloxacin-related hepatic toxicity prompted withdrawal of this fluoroquinolone from the market.

The excellent activity and substantial CSF penetration of the fluoroquinolones (20–60% of peak serum concentrations, even without meningeal inflammation or dexamethasone coadministration) may make them a promising option in pneumococcal meningitis caused by multi-resistant organisms in children. However, several drawbacks of this group of drugs should be kept in mind. The mutations that cause decreased susceptibility to the fluoroquinolones develop spontaneously at a frequency of 1 in 10⁶ to 10⁹. This rate is comparable with the development of resistance to rifampicin. In paediatric patients with pneumococcal meningitis, there maybe >10⁸/mL infecting organisms in the CSF. Thus, resistance may develop during treatment or as a result of exposure to a person who had been treated previously with a fluoroquinolone. The emergence of fluoroquinolone-resistant *S. pneumoniae* is rapidly increasing^[51,52] and routine susceptibility testing is currently not recommended. Thus, the choice of empirical therapy with a fluoroquinolone will be difficult. In addition, the use of fluoroquinolones in children with meningitis is currently not approved by the US FDA. Their usage

should be limited to patients where other antibacterials cannot be used or have failed.

Linezolid, an oxazolidinone, has been shown to be effective *in vitro* against multi-resistant Gram-positive organisms, including *S. pneumoniae*. Linezolid is only marginally bactericidal *in vitro* at concentrations five and ten times above the MIC. The penetration of the drug into ventricular fluid (which may equal lumbar CSF concentrations) was excellent even without inflammation.^[53] Little is known about the effectiveness of linezolid in pneumococcal CNS infections. There have been several reports of successful use of linezolid for vancomycin-resistant enterococcal meningitis.^[54,55] In the rabbit model, linezolid showed good penetration into the meninges but was less effective than ceftriaxone against penicillin-sensitive strains of *S. pneumoniae*.^[56] Linezolid had inferior killing rates against a penicillin-resistant strain of pneumococcus compared with combination therapy with ceftriaxone and vancomycin. Further investigation is required to determine if the use of linezolid for pneumococcal meningitis will be beneficial.

Chloramphenicol resistance among pneumococci was reported in 1970. Unfortunately, high rates of resistance were reported from many resource-poor countries (e.g. Southeast Asia and Africa) where chloramphenicol is affordable.^[57] In addition, unsatisfactory outcomes (due to poor bactericidal activity of this drug against pneumococci) were also reported when chloramphenicol was used to treat meningitis.^[58]

The recommended duration of therapy for uncomplicated pneumococcal meningitis, 10–14 days, is not based on scientific data. In the pneumococcal meningitis animal model, adequate CSF sterilisation was demonstrated after only 8 hours of penicillin therapy.^[59] A randomised clinical trial of 4 versus 7 days of ceftriaxone for uncomplicated bacterial meningitis resulted in effective treatment of all children with *S. pneumoniae* meningitis.^[60] Patients were followed for 3 months after hospital discharge, and none experienced neurological sequelae or relapse; however, the study was limited by a small sample size. Because shorter lengths of therapy

would be beneficial in areas where resources are limited, further studies are needed to evaluate if length of therapy for meningitis due to highly resistant pneumococcal strains can be shortened to ≤ 1 week.

3.2 *Haemophilus influenzae* Type B

The recommended initial therapy for Hib meningitis is a third-generation cephalosporin or chloramphenicol (table II).^[7] Empirical monotherapy with ampicillin is not recommended, as β -lactamase-producing strains of Hib account for up to 34% of isolates worldwide.^[6] In resource-poor countries, chloramphenicol continues to be widely used because of its availability and low cost. However, Hib resistance to chloramphenicol is well described.^[61,62] In addition, chloramphenicol was found to be inferior to cefotaxime and ceftriaxone in a prospective study.^[63] The third-generation cephalosporins have a significantly better efficacy and safety profile than chloramphenicol, and so ceftriaxone or cefotaxime are the drugs of choice in developed nations. The second-generation cephalosporins are not recommended as they have a slower rate of sterilisation and are associated with higher sequelae rate.^[64] Although cefepime^[65] and meropenem^[44] have shown efficacy and safety comparable with third-generation cephalosporins, they should be rarely used because clinical experience is limited, particularly in cases with *S. pneumoniae* resistant to penicillin and/or cefotaxime.

The recommended length of therapy for uncomplicated Hib meningitis in the US is 10 days.^[66] In a study comparing 7 with 10 days of therapy, 7 days was found to be just as effective treatment.^[67] In addition, in a study that compared 4 with 7 days of ceftriaxone for uncomplicated bacterial meningitis, there was no difference in clinical outcome between the two small treatment groups.^[60] Thus, the length of therapy can be shortened in most patients and the ultimate length of therapy should be individualised on the basis of the clinical response of each patient.

3.3 *Neisseria meningitidis*

Penicillin resistance in *N. meningitidis* has been documented worldwide.^[68-70] The majority of resistant isolates are moderately penicillin susceptible, with MIC values for penicillin of 0.12–1.0 $\mu\text{g/mL}$.^[71] High-dose benzylpenicillin (250 000 U/kg/day divided every 4–6 hours) is effective therapy against these moderately susceptible strains.^[71] However, it has been suggested that the outcome is poorer.^[72] Thus, a third-generation cephalosporin or chloramphenicol should be used for meningococcal meningitis until the penicillin susceptibility of the organism is available (table II). There have been no reports of treatment failure with third-generation cephalosporins. Chloramphenicol remains the first-line therapy in resource-poor countries because of its availability, low cost and ease of administration. Unfortunately, recent reports documented a high level of chloramphenicol resistance among meningococci.^[73] As sensitivity patterns continue to evolve, surveillance for resistant patterns must continue globally to document the distribution of resistant strains and, if necessary, to change recommendations for therapy.

The current recommended length of therapy for meningococcal meningitis is 7 days.^[71] However, significantly shorter courses of therapy have proven effective. A single dose of long-acting penicillin or chloramphenicol has each been used successfully.^[74,75] Additional studies found 3 or 4 days of antibacterial therapy to be effective.^[76,77]

4. Adjunctive Dexamethasone Therapy

The inflammatory process associated with bacterial meningitis is due to bacterial products that stimulate massive cytokine release into the subarachnoid space.^[3] This inflammatory response is important in the pathophysiology of bacterial meningitis and can lead to permanent neurological sequelae, including (most commonly) hearing loss. Various anti-inflammatory agents have been successful in reducing the harmful effect of the inflammatory response in animal models of bacterial meningitis.^[3] Currently, corticosteroids (given before or concomitantly with

antibacterials) are the only anti-inflammatory agent that have shown efficacy in humans.

The benefit of dexamethasone in the treatment of bacterial meningitis in children was evaluated in a meta-analysis of clinical trials published between 1988 and 1996.^[78] It was concluded that, for Hib meningitis, there was significant benefit of adjunctive dexamethasone (0.15 mg/kg every 6 hours for 2 days). This benefit was most significant regarding prevention of hearing loss. However, the benefit of dexamethasone for pneumococcal meningitis was not definitive. As Hib meningitis has now been virtually eradicated in the developed world, the empirical use of adjunctive corticosteroids in areas where pneumococci are the most common pathogen has been controversial. There are several reasons to question the suggested benefit of dexamethasone in pneumococcal meningitis. Several studies that were included in the meta-analysis by McIntyre et al.^[78] are questionable. For example, the Egyptian study had an unusually high mortality rate (28%) and children <5 years of age were not assessed for hearing loss.^[79] This study included 429 patients ranging in age from 3 months to 60 years (mean 12.5 years) but only 106 of these patients had pneumococcal meningitis. The authors observed a significant reduction in mortality and hearing impairment in patients with pneumococcal meningitis, but they did not specify if the observed effects of dexamethasone were in adults or children, or both. In addition, the Turkish study included only children >2 years of age, and the differences in moderate or severe hearing loss were statistically insignificant at 6 weeks' follow-up.^[80] This study enrolled 53 patients with pneumococcal meningitis (27 received dexamethasone and 26 received placebo). There were no differences between the two groups in mortality or neurological outcome. One patient with profound hearing loss (at 6 weeks' follow-up) who received dexamethasone was found to have a normal hearing at 3 months after discharge in the Turkish study. With this 'improvement', hearing impairment became significantly less in the dexamethasone group. The authors of the meta-analysis admitted that "the Egyptian study differed from others", and

that "the statistical significance of protection from early dexamethasone was vulnerable to exclusion of this study. Without the Egyptian study, the odds ratio for early dexamethasone became 0.3 (95% CI, 0.03–1.84; $p = 0.26$)";^[78] the statistical significance of a beneficial effect of dexamethasone is lost. In a retrospective study of 97 children with pneumococcal meningitis (41 of whom received dexamethasone and 56 who did not), no significant differences between the treatment groups were found in regard to presence of seizures, subdural effusions, hydrocephalus or death. In addition, no differences in neurological or audiological outcome were found at 6 weeks' and 4 months' follow-up. The number of survivors with any adverse outcome was smaller in patients who received corticosteroids within 24 hours of initiating antibacterials compared with those who never received corticosteroid therapy (4 of 35 vs 14 of 43, $p = 0.033$).^[81]

With the current recommended therapy of vancomycin and a third-generation cephalosporin, the benefit of dexamethasone in the treatment of pneumococcal meningitis is even more in doubt. As dexamethasone is an anti-inflammatory agent, it significantly reduces the ability of some antibacterials to cross the BBB, leading to diminished CSF antibacterial concentrations. In animal models, vancomycin concentrations in the CSF were reduced by 44–77% when administered with dexamethasone.^[40,82] As a result, a delay in CSF sterilisation was observed in the animals treated with dexamethasone. The concern about the diminished CNS penetration of vancomycin in patients receiving adjunctive corticosteroids led to the recommendation in adults that rifampicin be preferred over vancomycin if dexamethasone is used.^[83]

Recently, De Gans and Van de Beek^[8] concluded that early treatment with dexamethasone improved the overall clinical outcome of adults with bacterial meningitis. Extrapolation of this study's results to paediatric patients is difficult. First, all of the pneumococcal isolates available for susceptibility testing (72%) in this trial were penicillin-sensitive; no patient was treated with vancomycin. In addition, there was no significant beneficial effect on neurological

sequelae, including hearing loss, which is a major concern in the paediatric population. Secondly, pneumococcal meningitis in adults is different from that in paediatric patients both by the predisposing or associated conditions and by the spectrum of complications and outcome.^[84] In general, fatalities are less frequent in children than in adults, and any attempt to extrapolate from the De Gans and Van de Beek study to paediatric patients must take these differences into account.

Several other observations suggest that any decision to add dexamethasone to the current recommended therapy for pneumococcal meningitis should be made with caution. A 3-year multicentre retrospective study of pneumococcal meningitis (from 1993 to 1996), which included 40 children who had received dexamethasone (initiated before or within 1 hour after the initiation of antibacterials), showed that the incidence of moderate-to-severe hearing loss was significantly higher in the dexamethasone group (46%) compared with the group who did not receive any corticosteroids (23%).^[34] However, the children who received dexamethasone were more critically ill, with more abnormal CSF parameters on presentation. When such factors were controlled for, the incidence of neurological sequelae between the two groups was no longer statistically significant.

The largest placebo-controlled, double-blind, randomised trial of adjunctive dexamethasone therapy for bacterial meningitis was performed in Malawi by Molyneux et al.^[85] This study included 598 children (aged 2 months to 13 years old); 51% received dexamethasone, while 49% received placebo. Five to ten minutes after adjunctive therapy was given, patients were treated with benzylpenicillin and chloramphenicol. The aetiological agents included *S. pneumoniae* (40%), Hib (28%), *N. meningitidis* (11%) and *Salmonella* species (5%). Thirteen percent of patients had negative CSF cultures. Of the 229 pneumococcal isolates, 39 (17%) were resistant to chloramphenicol and 47 (20%) were resistant to penicillin. Comorbidities in this population included HIV infection, malnutrition and anaemia. In comparing the outcome of both groups, there

was no difference in survival or neurological sequelae. It was concluded that corticosteroids are not an effective adjuvant in the treatment of acute bacterial meningitis in resource-poor countries. The relevance of the outcome of this study in a resource-poor country is not clear regarding paediatric care in developed countries or in developing countries with better health systems than Malawi.

Recently, two studies using different animal models showed increased hippocampal neuronal apoptosis when dexamethasone was added to treatment of pneumococcal meningitis.^[86,87] Furthermore, dexamethasone therapy was associated with reduced learning capacity and spatial memory.^[87] If a large prospective, randomised, placebo-controlled trial to evaluate the use of dexamethasone in pneumococcal meningitis is performed, it should assess all the possible effects of the drug on the CNS and not only hearing loss. Taking into account this information, recommendations regarding dexamethasone treatment should be made with maximum caution. With the current pneumococcal vaccination recommendations to prevent invasive infections and the resultant decreased incidence of pneumococcal meningitis, the need to make this difficult decision may become a rare event.

5. Other Adjunctive Anti-inflammatory Agents

Currently, dexamethasone is the only anti-inflammatory agent extensively studied and used, both in experimental models and in clinical paediatric trials. There are several other anti-inflammatory agents that have been reported as possible adjunctive therapy for bacterial meningitis, all with the common goal of reducing brain injury. Such experimental therapies, studied in animal meningitis models, include: NSAIDs such as ketorolac, which, with ampicillin, reduced sensorineural hearing loss compared with placebo;^[88] monoclonal antibody against tumour necrosis factor- α , which lowered intracranial pressure and reduced CSF pleocytosis;^[89] and the bradykinin receptor antagonist labradimil (RMP-7), which increases BBB permeability at the endothelial tight junctions and improves the CNS penetration of

both antimicrobials and chemotherapeutics.^[90] Induced hypothermia has also been evaluated as adjunctive treatment to decrease intracranial pressure and cerebral oedema;^[91] similar hypothermic treatment has been proposed for patients with traumatic brain injury. As all of these adjunctive treatments are considered experimental, none is currently recommended for the treatment of patients with bacterial meningitis.

6. Other Considerations

6.1 Syndrome of Inappropriate Antidiuretic Hormone Secretion

Hyponatraemia, which commonly occurs in bacterial meningitis, can worsen the course of the disease and its outcome.^[92] Because the secretion of antidiuretic hormone in most of these children was found to be increased (Syndrome of Inappropriate Antidiuretic Hormone Secretions; SIADH), it was assumed that retention of body water due to this hormone is the cause of the hyponatraemia. As a result, fluid restriction (two-thirds of usual maintenance) has been widely advocated and used. For example, Duke and Molyneux^[93] suggested that administration of 0.9% saline (with 5% dextrose) at less than maintenance volume will result in lower frequency of hyponatraemia and neurological events. In recent years this practice was challenged because it was shown that many of these children were dehydrated^[94] and/or hypovolaemic^[95] for other reasons (e.g. vomiting, diminished intake, diarrhoea). In addition, Singhi et al.^[96] showed that routine fluid restriction did not improve the outcome and may be associated with a higher mortality rate in those children who had reduction in extracellular water of >10 mL/kg because of fluid restriction during the initial 48 hours of medical therapy. Therefore, only a selected group of patients (those with hyponatraemia clearly due to SIADH) may benefit from fluid restriction. The diagnosis of SIADH should be based on the following strict criteria (as described by Bartter and Schwartz^[97]): (i) hyponatraemia with corresponding hypo-osmolality of the serum and extracellular fluid; (ii) continued renal

excretion of sodium; (iii) absence of chemical evidence of volume depletion; (iv) osmolality of urine greater than that appropriate for the concomitant tonicity of the plasma; (v) normal renal function; and (vi) normal adrenal function. Empirical fluid restriction in all patients with bacterial meningitis should be avoided. Only patients with a diagnosis of 'true' SIADH (based on these criteria) or developing increased intracranial pressure should be treated with fluid restriction.

6.2 Prophylaxis

The secondary attack rate of *N. meningitidis* in households of an index case is about 3 per 1000, a rate 1000 times the attack rate in the general population.^[98] Because of this significantly increased risk, chemoprophylaxis is recommended for household contacts of an index case and for others with close contact. For healthcare workers, prophylaxis is indicated only when intimate exposure with nasopharyngeal secretions occurred, such as mouth-to-mouth resuscitation or endotracheal intubation. Individuals in close contact with the index case up to 7 days before onset of illness should be considered for prophylaxis.^[71]

There are three recommended agents for chemoprophylaxis against *N. meningitidis* (table III). A fourth drug, sulfadiazine, which was the original drug used for meningococcal chemoprophylaxis, is no longer recommended because of the emergence of sulfa-resistant strains. Oral rifampicin is currently the drug of choice for chemoprophylaxis in the paediatric population. Alternatives include a single

Table III. Recommended chemoprophylaxis for high-risk contacts of people with invasive meningococcal disease

Medication (age group)	Dose	Duration
Rifampicin ^a (≤1 month)	5 mg/kg orally every 12 hours	2 days
Rifampicin (>1 month)	10 mg/kg orally every 12 hours (maximum 600mg)	2 days
Ceftriaxone (≤15 years)	125mg intramuscularly	1 dose
Ceftriaxone (>15 years)	250mg intramuscularly	1 dose
Ciprofloxacin ^b	500mg orally	1 dose

a Not recommended for use in pregnant women.

b Not approved for use in patients <18 years of age.

intramuscular dose of ceftriaxone or a single dose of oral ciprofloxacin. The use of fluoroquinolones is not approved for pregnant women and children.

Unfortunately, rifampicin resistance among *N. meningitidis* was reported in Israel in the mid-1990s^[99] and has been recently reported in the US;^[100] increasing rifampicin resistance may have significant public health impact, as it is the sole oral agent recommended in the paediatric population.

The benefit of chemoprophylaxis to prevent the spread of Hib is controversial.^[101,102] Yet, the AAP^[66] recommends chemoprophylaxis for households in the following circumstances: (i) if there is at least one contact <4 years of age who is not immunised or incompletely immunised; (ii) if there is a child <12 months of age that has not received the primary series; or (iii) if there is an immunocompromised child in the household (regardless of immunisation status). Chemoprophylaxis is also indicated for nursery school and child care contacts, regardless of age, when two or more cases of Hib invasive disease have occurred within 60 days, and for the index case, if <2 years of age or a member of a household with a susceptible contact and treated with a regimen other than cefotaxime or ceftriaxone. In the latter instance, chemoprophylaxis should be given at the time of hospital discharge. Rifampicin, which eradicated 95% of nasopharyngeal carriage,^[103] is recommended (20 mg/kg/day twice daily for 2 days; maximum dose 600mg).

6.3 Vaccination

The overwhelming success of Hib vaccination in the developed world is an example of the impact that immunisation can have on the disease. For *S. pneumoniae*, a 23-valent polysaccharide vaccine has been available for many years and is useful in preventing invasive disease in the elderly population. However, this vaccine is poorly immunogenic in children younger than 2 years of age, in whom the highest proportion of invasive pneumococcal disease occurs. In 2000, a pneumococcal vaccine was introduced which contains seven capsular polysaccharide antigens, each of which is conjugated to a diphtheria protein (cross-reactive material

CRM197). This protein-conjugated vaccine elicits an adequate T cell-dependent response in young children, thus protecting this vulnerable population against the seven strains of pneumococci most associated with invasive disease. As noted in section 1, a significant reduction in paediatric invasive pneumococcal disease has already been demonstrated, especially in children <2 years of age.^[12,104] Both 9- and 11-valent conjugated pneumococcal vaccines are currently under investigation.^[11]

Primary prevention of meningococcal disease is essential; the disease may be so fulminant on presentation that medical therapy (including antibacterials) makes no impact on the course of the disease. Thus, purified capsular polysaccharide vaccines against *N. meningitidis* serogroups A, C, Y and W135 have been developed. They are available as monovalent A and C, bivalent A/C and quadrivalent A/C/Y/W135 vaccines; the quadrivalent polysaccharide is the only vaccine that is licensed and available in the US. Group A vaccine is effectively immunogenic in all age groups. This vaccine has been effective in terminating epidemics of group A disease.^[105] The recent introduction of conjugate group C vaccine in the UK resulted in an approximately 80% reduction in the incidence of group C disease.^[106] In addition, a herd immunity (i.e. reduction in attack rate of unvaccinated people) was documented.^[107] Unfortunately, no vaccine exists against serogroup B, as the capsular polysaccharide of this serogroup is not immunogenic in humans. Development of a vaccine against serogroup B remains a priority, and investigational trials continue. Intranasal administration of a meningococcal outer membrane vesicle vaccine was shown to induce persistent local and serum antibodies.^[108] Two outer membrane meningococcal B vaccines, developed in Cuba and Norway, were found to be useful during epidemics with a single circulating serotype B.^[109,110] Such a vaccine is also being evaluated in New Zealand, where a meningococcal B epidemic is ongoing since 1991.^[111] Unfortunately, this vaccine will not be useful for routine immunisation because many endemic areas have multiple B serosubtypes (i.e. heterogeneous) and the protection provided by

the vaccine will be limited to the substrain from which it was developed. Others are attempting to develop an immunogenic vaccine by chemically modifying the polysaccharide and conjugating it to an immunogenic protein carrier.^[112] This vaccine is currently undergoing clinical trials.

Since 1987, Saudi Arabia health authorities require compulsory vaccination with the bivalent A and C vaccine for all Hajj pilgrims and annual vaccination campaigns for all local populations living in pilgrimage sites. However, in the past several years serogroup W135 has emerged, including an outbreak of >300 cases in Saudi Arabia and nine other countries among the Hajj pilgrims or their close contacts.^[113] As a result, vaccination policies since 2002 include the quadrivalent vaccine for both local residents and Hajj pilgrims.

Routine childhood vaccination with the quadrivalent vaccine is not recommended because of its low immunogenicity in young children.^[114] The AAP recommends vaccination of those who have functional or anatomic asplenia, terminal complement component or properdin deficiencies, and college students who live in dormitories.^[71]

7. Conclusions

Despite advances in antibacterial therapy and vaccine development, bacterial meningitis remains a significant cause of morbidity and mortality in paediatric patients. Resource-poor countries continue to face the hardship of economic constraints, unable to offer the benefits of vaccine technology. Hib remains a significant cause of disease in these countries, while its incidence has dramatically decreased in the developed world as a result of widespread vaccination. In developed countries, advances in pneumococcal and meningococcal vaccination are likely to lead to similar trends.

Resistance patterns to currently available antibacterials continue to evolve. As a result, clinicians must remain vigilant in detecting the emergence of new resistant strains. The continued development of new and effective antibacterials for bacterial meningitis is greatly needed. In addition, we must continue to evaluate the possible usefulness of adjunctive

anti-inflammatory agents as dexamethasone use remains controversial in pneumococcal meningitis.

The widespread availability of preventive vaccines against the common pathogens of bacterial meningitis is the ultimate goal; until this goal is reached, timely diagnosis and treatment is paramount to minimise morbidity and mortality.

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