Bacterial Meningitis 2

Advances in treatment of bacterial meningitis

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Bacterial meningitis kills or maims about a fifth of people with the disease. Early antibiotic treatment improves outcomes, but the effectiveness of widely available antibiotics is threatened by global emergence of multidrug-resistant bacteria. New antibiotics, such as fluoroquinolones, could have a role in these circumstances, but clinical data to support this notion are scarce. Additionally, whether or not adjunctive anti-inflammatory therapies (eg, dexamethasone) improve outcomes in patients with bacterial meningitis remains controversial; in resource-poor regions, where the disease burden is highest, dexamethasone is ineffective. Other adjunctive therapeutic strategies, such as glycerol, paracetamol, and induction of hypothermia, are being tested further. Therefore, bacterial meningitis is a substantial and evolving therapeutic challenge. We review this challenge, with a focus on strategies to optimise antibiotic efficacy in view of increasingly drug-resistant bacteria, and discuss the role of current and future adjunctive therapies.

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This is the second in a **Series** of three papers about bacterial meningitis

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Introduction

Acute bacterial meningitis is a life-threatening infectious disease, the epidemiology of which has changed substantially since the introduction of conjugate vaccines.[1–3] Nevertheless, the disease continues to inflict a heavy toll, including in high-income countries, causing substantial morbidity and mortality.[1,4] Early administration of antibiotics saves lives, but the global emergence of multidrug-resistant bacteria threatens the effectiveness of many inexpensive and widely available antibiotics. The role of adjunctive anti-inflammatory therapies is uncertain, especially in resource-poor settings. For these reasons, bacterial meningitis is an evolving therapeutic challenge. In this review, we discuss the various treatment strategies available, and draw attention to advances in antibiotic and adjunctive therapy.

Initial empirical antibiotics

Early clinical suspicion of bacterial meningitis and rapid administration of antibiotics is important to increase survival and reduce morbidity. In a prospective study of 156 patients with pneumococcal meningitis admitted to an intensive-care unit,[5] a delay in antibiotic treatment of longer than 3 h after arrival at the hospital was associated with increased 3-month mortality.

Administration of empirical antibiotics for patients with bacterial meningitis should be based on local epidemiology, the patient's age, and the presence of specific underlying diseases or risk factors (table 1).[4,6] In geographical regions with *Streptococcus pneumoniae* (pneumococcal) strains that are resistant to penicillin and cephalosporins (figure), patients older than 1 month with community-acquired bacterial meningitis should receive vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone). The decision of whether to use vancomycin depends on the rate of resistance to third-generation cephalosporins. In areas where the prevalence of cephalosporin-resistant *S pneumoniae* is low (<1% resistance), a third-generation cephalosporin (either cefotaxime or ceftriaxone) usually suffices as empirical therapy. Furthermore, vancomycin is expensive and rarely available in low-income countries.[7] Alternative agents in these settings include an antipneumococcal fluoroquinolone (eg, moxifloxacin) and rifampicin, although clinical data to support the use of these drugs are scarce. Rifampicin is inexpensive, widely available, penetrates reasonably well into cerebrospinal fluid (CSF), and usually has in-vitro activity against ceftriaxone-resistant pneumococcal strains.[4,8]

Listeria monocytogenes is noteworthy because of its resistance to cephalosporins. Amoxicillin or ampicillin are effective against *Listeria* spp and should be given to immunosuppressed patients with meningitis who are at risk of this infection, including pregnant patients and those older than 50 years.

Optimisation of the delivery and effectiveness of antibiotics

Optimisation of the delivery and effectiveness of antibiotics are two key therapeutic challenges in bacterial meningitis. Penetration across the blood–brain barrier is important for successful treatment and depends on the amount of disruption of the barrier's integrity by inflammation, and the size, charge, lipophilicity, protein-binding ability, and interaction with efflux pumps of the antibiotic (table 2).[8,9] However, clinical efficacy also

Search strategy and selection criteria

We searched the Cochrane Library (The Cochrane Library 2011, issue 1), Medline (1966 to March, 2012), and Embase (1974 to March, 2012). We used the search terms "bacterial meningitis" or "meningitis" with the terms "therapy" or "antibiotics" or "antimicrobial" or "treatment". We mainly selected articles published in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those that we judged to be relevant. Review articles and book chapters are cited to provide readers with more details and more references than can be included in this paper. We modified our reference list on the basis of comments from peer reviewers.

	Bacterial pathogens	Empirical therapy	Intravenous dose (dose interval)
Community-acquired meningitis			
Age <1 month	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes*	Amoxicillin/ampicillin plus cefotaxime, or amoxicillin/ampicillin plus an aminoglycoside	Age <1 week: ampicillin 150 mg/kg per day (8 h); cefotaxime 100–150 mg/kg per day (8–12 h); gentamicin 5 mg/kg per day (12 h) Age 1–4 weeks: ampicillin 200 mg/kg per day (6–8 h); gentamicin 7·5 mg/kg per day (8 h); tobramycin 7·5 mg/kg per day (8 h); amikacin 30 mg/kg per day (8 h); cefotaxime 150–200 mg/kg per day (6–8 h)
Age 1–23 months	*S agalactiae, E coli, S pneumoniae, Neisseria meningitidis*	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)*	Vancomycin 60 mg/kg per day (6 h) to achieve serum trough concentrations of 15–20 μg/mL; cefotaxime 225–300 mg/kg per day (6–8 h); ceftriaxone 80–100 mg/kg per day (12–24 h)
Age 2–50 years	*S pneumoniae, N meningitidis*	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)*	Children as above; adults: vancomycin 30–60 mg/kg per day (8–12 h) to achieve serum trough concentrations of 15–20 μg/mL; ceftriaxone 4 g per day (12 h); cefotaxime 8–12 g per day (4–6 h); cefepime 6 g per day (8 h); ceftazidime 6 g per day (8 h); amoxicillin or ampicillin 12 g per day (4 h); penicillin 24 million units per day (4 h); meropenem 6 g per day (8 h)
Age >50 years	*S pneumoniae, N meningitidis, L monocytogenes,* aerobic Gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)	As for adults above
Immunocompromised state	*S pneumoniae, N meningitidis, L monocytogenes, Staphylococcus aureus, Salmonella* spp, aerobic Gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin plus ampicillin plus either cefepime or meropenem	..
Recurrent	*S pneumoniae, N meningitidis, Haemophilus influenzae*	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)	..
Health-care-associated meningitis			
Basilar skull fracture	*S pneumoniae, H influenzae,* group A β-haemolytic streptococci	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)	..
Head trauma; post-neurosurgery	Staphylococci (*S aureus* and coagulase-negative staphylococci), aerobic Gram-negative bacilli (including *P aeruginosa*)	Vancomycin plus ceftazidime, cefepime, or meropenem	..

Preferred daily intravenous doses (and dosing intervals) apply to patients with normal renal and hepatic function. In patients with impaired renal function, the loading (initial) dose of the antibiotic is based on the extracellular fluid volume and is not changed in the case of decreased renal function; subsequent doses or dosing intervals need to be changed in patients with impaired renal function. *Add amoxicillin or ampicillin if meningitis caused by *L monocytogenes* is also suspected.

Table 1: **Empirical antibiotics for presumed bacterial meningitis by demography and risk factor**

depends on the antibiotic CSF concentration and its bactericidal activity against causative bacteria.[8] For example, although β-lactam antibiotics penetrate poorly into the CSF, very effective bactericidal concentrations can be achieved by administration of frequent and high systemic doses, which are generally well tolerated.[8] Toxicity makes dose escalation difficult for the aminoglycosides, glycopeptides, and polymyxins; therefore, intrathecal or intraventricular administration of these agents might be needed to reach effective CSF concentrations, although data to support the safety and efficacy of this approach are scarce.[10] The intrathecal route resulted in high CSF aminoglycoside concentrations in young children with gram-negative meningitis,[11] but a controlled, non-randomised study of intrathecal versus intravenous gentamicin in 117 infants with Gram-negative meningitis did not show clinical benefit.[12] Furthermore, in a randomised controlled trial of intraventricular versus systemic gentamicin, investigators reported a substantially higher mortality rate in patients receiving intraventricular gentamicin therapy (43% *vs* 13%).[13]

A better understanding of the relation between CSF concentration and antibiotic effectiveness could improve clinical outcomes. Almost 60 years ago, Eagle and colleagues[14] showed that penicillin killed bacteria more effectively when given continuously rather than by bolus injections; the best predictor of successful treatment was the time that concentrations were maintained above the minimum inhibitory concentration (MIC). Some studies have investigated whether continuous infusions of these antibiotics improve outcomes in patients with bacterial meningitis.[15] A possible benefit of continuous cefotaxime infusion was suggested in a study of 723 African children with bacterial meningitis randomly assigned to either cefotaxime boluses or continuous cefotaxime infusion for the first 24 h of therapy;[16] 272 (38%) children died, but the mode of cefotaxime administration did not significantly change the proportion of children who died or were severely disabled by hospital discharge. However, a planned subgroup analysis showed that children with pneumococcal meningitis given continuous cefotaxime infusion were significantly less likely to die or have sequelae than were those given cefotaxime boluses.

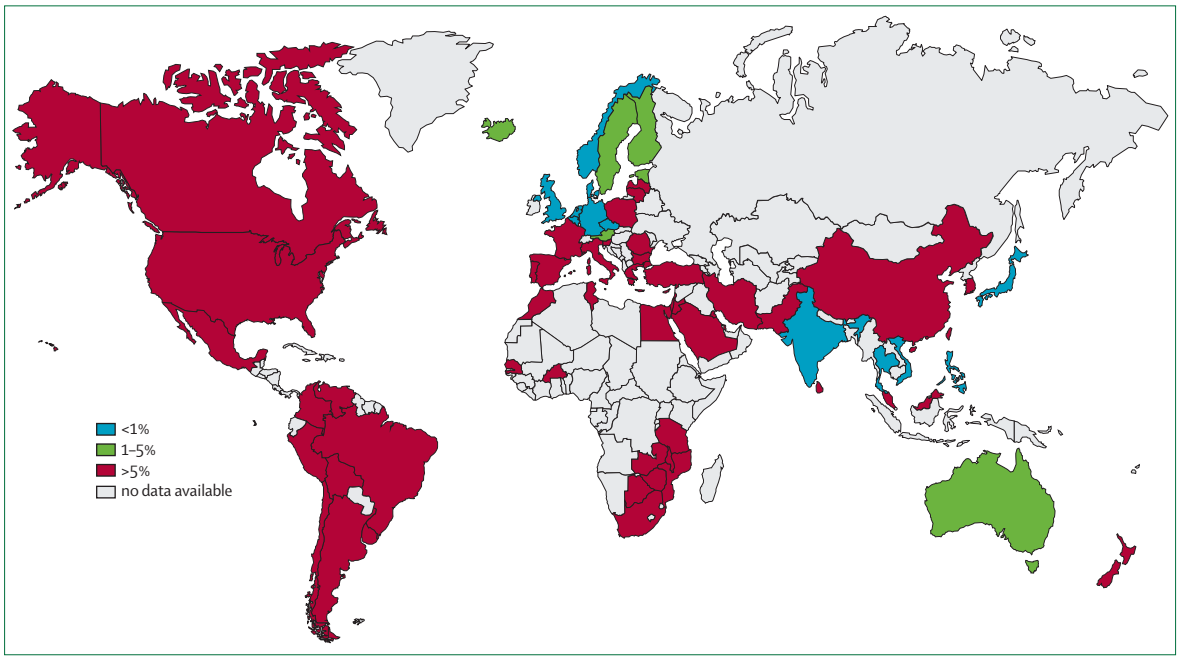

Figure: Global rates of pneumococcal penicillin resistance

Antibiotics for specific organisms

Once a bacterial pathogen has been identified on a CSF Gram stain, or isolated and in-vitro susceptibility testing done, antibiotic therapy can be modified further for optimum treatment (tables 3 and 4).

Streptococcus pneumoniae

The treatment of pneumococcal meningitis has changed since the emergence of strains with reduced susceptibility to penicillin (figure); the prevalence of reduced susceptibility ranges from 25% to more than 50% in some US regions and is even higher in many other countries.[17] Penicillin resistance is a marker of decreased susceptibility to other antibiotics, which could lead to treatment failures in patients with pneumococcal meningitis.[18] In areas with cephalosporin resistance, empirical therapy for pneumococcal meningitis should consist of vancomycin combined with either cefotaxime or ceftriaxone, pending results of in-vitro susceptibility testing. Although rates of pneumococcal meningitis have decreased since the introduction of the heptavalent pneumococcal conjugate vaccine, the number of patients with meningitis caused by serotypes not covered by the vaccine, including resistant strains, has increased.[19] Non-vaccine serotypes are generally more susceptible to antibiotics than are vaccine serotypes, except for serotype 19A.[19]

Adequate doses of vancomycin are important to achieve appropriate CSF concentrations, because concomitant use of adjunctive dexamethasone could reduce vancomycin penetration into CSF. In a study of 14 patients with bacterial meningitis who were receiving adjunctive dexamethasone, administration of intravenous vancomycin (15 mg/kg loading dose, followed by a continuous infusion of 60 mg/kg per day), led to adequate CSF vancomycin concentrations (mean 7·9 μg/mL).[20] Although clinical data on the efficacy of rifampicin in patients with pneumococcal meningitis are scarce, some authorities use this agent in combination with a third-generation cephalosporin, with or without vancomycin, in patients with pneumococcal meningitis caused by strains that are likely to be highly resistant to penicillin or cephalosporins.[4]

Once the MIC of penicillin and third-generation cephalosporins is known, treatment can be modified accordingly (table 4). The Clinical and Laboratory Standards Institute has redefined the in-vitro susceptibility breakpoints for pneumococcal isolates from patients with meningitis as either susceptible (MIC ≤0·06 μg/mL) or resistant (MIC ≥0·12 μg/mL) to penicillin;[21] for penicillin-resistant strains, the therapeutic approach depends on the degree of in-vitro susceptibility to the third-generation cephalosporins.

Neisseria meningitidis

The current treatment recommendation for meningococcal meningitis is penicillin G, amoxicillin, or ampicillin.[3,4,6] However, meningococcal strains with reduced susceptibility to penicillin have been identified in many countries. In a Spanish study,[22] the investigators reported an increase in the prevalence of meningococcal strains with reduced susceptibility to penicillin from 9·1% in 1986, to 71·4% in 1997. By contrast, intermediate susceptibility to penicillin (MIC >0·1 μg/mL) has been reported in 3–4% of US meningococcal isolates and 2% of isolates in sub-Saharan Africa.[23,24] In one study,[25] investigators recorded an association between reduced susceptibility to

	CSF penetration (CSF:plasma)* in uninflamed meninges	CSF penetration (drug in CSF:plasma)* in inflamed meninges	Comments on use of antibiotic class for meningitis treatment
β-lactams			Poor CSF penetration, but high systemic doses are well tolerated and attain CSF concentrations that greatly exceed the MIC of susceptible bacteria. 40% of cefotaxime *vs* 90% of ceftriaxone is protein bound. Avoid imipenem because it could lower the seizure threshold. Continuous infusions could enhance bacterial killing
Benzylpenicillin	0·02	0·1	
Amoxicillin/ampicillin	0·01	0·05	
Cefotaxime	0·1	0·2	
Ceftriaxone	0·007	0·1	
Meropenem	0·1	0·3	
Aminoglycosides			Poor CSF penetration and toxicity limits increases in systemic doses. Consider intraventricular/intrathecal delivery if needed
Gentamicin	0·01	0·1	
Amikacin	No data	0·1	
Glycopeptides			Poor CSF penetration and toxicity limits increases in systemic doses. Continuous infusions could enhance bacterial killing. Limited data for intraventricular/intrathecal delivery
Vancomycin	0·01	0·2	
Teicoplanin	0·01	0·1	
Fluoroquinolones			Good CSF penetration. Moxifloxacin is an alternative agent for the treatment of penicillin-resistant pneumococcal meningitis
Ciprofloxacin	0·3	0·4	
Moxifloxacin	0·5	0·8	
Levofloxacin	0·7	0·8	
Others			
Chloramphenicol	0·6	0·7	Excellent CSF penetration, although toxicity concerns limit its use
Rifampicin	0·2	0·3	80% protein bound; CSF concentrations greatly exceed MIC of susceptible bacteria
Newer agents			
Cefepime	0·1	0·2	Effective against penicillin-resistant pneumococcal meningitis
Linezolid	0·5	0·7	Case report/series suggest effectiveness for pneumococcal, staphylococcal, and enterococcal meningitis, although high interindividual variability in CSF pharmacokinetics suggests therapeutic drug measurements could be needed
Daptomycin	No data	0·05	Poor penetration, but CSF concentrations exceed MIC of susceptible bacteria; case reports/series suggest efficacy in staphylococcal and enterococcal meningitis
Tigecycline	No data	0·5	Good CSF penetration, but concentrations achieved at current standard doses could be insufficient to ensure bacterial killing

CSF=cerebrospinal fluid. MIC=minimum inhibitory concentration. *Based on calculated area under the curve $(AUC)_{CSF}/AUC_{plasma}$ when possible, but data are limited for most antibiotics and AUC cannot be calculated on the basis of single CSF measurements. In these circumstances, CSF penetration is estimated from paired plasma and CSF measurements.

***Table 2*: Estimates of CSF penetration of antibiotics used for the treatment of bacterial meningitis[8,9]**

	Antibiotic therapy
Gram-positive cocci in pairs	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)
Gram-negative cocci in pairs	Third-generation cephalosporin (either cefotaxime or ceftriaxone)
Gram-positive bacilli	Amoxicillin/ampicillin* or penicillin G*
Gram-positive cocci in chains	Amoxicillin/ampicillin or penicillin G*
Gram-negative bacilli	Third-generation cephalosporin

*Consider the addition of an aminoglycoside.

***Table 3*: Recommended antibiotics in patients with community-acquired meningitis by result of cerebrospinal fluid Gram stain**

penicillin and an increased risk of death or neurological sequelae in children with meningococcal meningitis. Therefore, patients with meningococcal meningitis should be treated empirically with a third-generation cephalosporin (cefotaxime or ceftriaxone) until results of in-vitro susceptibility testing are available. High-level resistance to chloramphenicol (MIC ≥64 μg/mL) has been reported,[26] but the incidence is low in most countries.[27] Furthermore, ciprofloxacin resistance has been described in some regions of the USA,[28] and has affected recommendations for chemoprophylaxis. During meningococcal meningitis epidemics in resource-poor settings, one intramuscular injection of long-acting chloramphenicol is sufficient;[27] an injection of ceftriaxone is equally effective.[29]

Listeria monocytogenes

Amoxicillin, ampicillin, or penicillin G is the treatment of choice for *Listeria* meningitis.[30] Some authorities have recommended the addition of an aminoglycoside because of enhanced in-vitro killing and in-vivo synergy in animal models. No study has been done to compare amoxicillin or ampicillin alone versus amoxicillin or

ampicillin plus gentamicin, although retrospective clinical data suggest that the addition of gentamicin can reduce mortality.[31] By contrast, in a cohort of 118 patients with listeriosis, the aminoglycoside-treated group had increased rates of kidney injury and mortality.[32] Trimethoprim-sulfamethoxazole is an alternative treatment in patients who are allergic to or intolerant of penicillin. In a retrospective study,[33] treatment with trimethoprim-sulfamethoxazole plus ampicillin was associated with a lower antibiotic failure rate and fewer neurological sequelae than was the combination of ampicillin plus an aminoglycoside.

Streptococcus agalactiae

The standard approach to the treatment of meningitis caused by group B streptococci is amoxicillin or ampicillin or penicillin G combined with an aminoglycoside.[4] Vancomycin and third-generation cephalosporins are alternatives. Some group B streptococci are less sensitive to penicillin (MIC 0·12–1·0 μg/mL) than others; the optimum regimen for these isolates is not clear and the efficacy of the third-generation cephalosporins in this setting has not been established.[34]

Haemophilus influenzae

Since the emergence of β-lactamase-producing and chloramphenicol-resistant strains of *H influenzae*, third-generation cephalosporins have become standard treatment. Third-generation cephalosporins are more effective than second-generation cephalosporins (eg, cefuroxime)[35] and chloramphenicol, even in patients with *H influenzae* type b meningitis caused by chloramphenicol-sensitive strains.[36] The rates of isolation of β-lactamase-producing strains vary worldwide (15% in the UK, 26% in the USA, 31% in France, and 42% in Spain), with high rates (42%) for non-typeable strains in the USA.[4] Chloramphenicol resistance is also a concern in resource-poor settings, where the drug is often used as first-line therapy for patients with bacterial meningitis. In Japan, the prevalence of β-lactamase-negative ampicillin-resistant *H influenzae* meningitis has increased rapidly from 6% in 2000 to 35% in 2004; many of these strains are also resistant to ceftriaxone.[37]

Aerobic Gram-negative bacilli

The emergence of multidrug-resistant Gram-negative bacilli is worrying, especially in patients with health-care-associated bacterial meningitis.[9] Resistance to the third-generation and fourth-generation cephalosporins, and carbapenems, has reduced the range of antibiotic options available. Outbreaks of meningitis caused by *Escherichia coli* strains producing extended-spectrum β-lactamases in neonatal wards can be difficult to control.[38] In patients with *Acinetobacter baumannii* meningitis, the most commonly used empirical antibiotic is meropenem with or without gentamicin or amikacin given either intraventricularly or intrathecally.[9] If the organism is resistant to carbapenems, colistin (usually formulated as colistimethate sodium) or polymyxin B should be given intravenously, and might be given by the intrathecal or intraventricular route. In one retrospective study of 51 patients with *Acinetobacter* meningitis,[39] all eight patients given a combination of intravenous and intrathecal colistin survived.

Staphylococcus aureus

S aureus meningitis occurs mainly after neurosurgical procedures or placement of CSF shunts.[9] Treatment

	Recommended therapy	Alternative therapies
Streptococcus pneumoniae		
Penicillin MIC ≤0·06 μg/mL	Penicillin G or amoxicillin/ampicillin	Cefotaxime, ceftriaxone, chloramphenicol
Penicillin MIC ≥0·12 μg/mL		
Cefotaxime or ceftriaxone MIC† <1·0 μg/mL	Cefotaxime or ceftriaxone	Cefepime, meropenem
Cefotaxime or ceftriaxone MIC† ≥1·0 μg/mL	Vancomycin plus either cefotaxime or ceftriaxone‡	Vancomycin plus moxifloxacin§
Neisseria meningitidis		
Penicillin MIC <0·1 μg/mL	Penicillin G or amoxicillin/ampicillin	Cefotaxime, ceftriaxone, chloramphenicol
Penicillin MIC ≥0·1 μg/mL	Cefotaxime or ceftriaxone	Cefepime, chloramphenicol, fluoroquinolone, meropenem
Listeria monocytogenes	Amoxicillin/ampicillin or penicillin G¶	Trimethoprim-sulfamethoxazole
Streptococcus agalactiae	Amoxicillin/ampicillin or penicillin G¶	Cefotaxime, ceftriaxone, vancomycin
Haemophilus influenzae		
β-lactamase negative	Amoxicillin/ampicillin	Cefotaxime, ceftriaxone, cefepime, chloramphenicol, aztreonam, fluoroquinolone
β-lactamase positive	Cefotaxime or ceftriaxone	Cefepime, chloramphenicol, aztreonam, fluoroquinolone
β-lactamase negative, ampicillin resistant	Meropenem	Fluoroquinolone
Staphylococcus aureus		
Meticillin sensitive	Nafcillin or oxacillin	Vancomycin, linezolid, daptomycin
Meticillin resistant‖	Vancomycin	Trimethoprim-sulfamethoxazole, linezolid, daptomycin
Staphylococcus epidermidis‖	Vancomycin	Linezolid
Enterobacteriaceae**	Cefotaxime or ceftriaxone	Aztreonam, fluoroquinolone, trimethoprim-sulfamethoxazole, meropenem, ampicillin
Pseudomonas aeruginosa	Ceftazidime or cefepime¶	Aztreonam, meropenem, ciprofloxacin¶
*Acinetobacter baumannii***	Meropenem	Colistin (usually formulated as colistimethate sodium), polymyxin B††

MIC=minimum inhibitory concentration. *In the absence of clinical data, recommendations for use of some agents are based on cerebrospinal fluid penetration and efficacy in experimental animal models of bacterial meningitis. †In-vitro activities of β-lactam antibiotic agents against *S pneumoniae* are predictable within drug classes, but the relation between penicillin and cefotaxime-ceftriaxone MICs is not linear. ‡Addition of rifampicin can be considered if the organism is susceptible, the expected clinical or bacteriological response is delayed, or the cefotaxime/ceftriaxone MIC of the pneumococcal isolate is >4·0 μg/mL. §No clinical data exist for use of this agent in patients with pneumococcal meningitis; recommendation is based on cerebrospinal fluid penetration and in-vitro activity against *S pneumoniae*. ¶Addition of an aminoglycoside should be considered; might need intraventricular or intrathecal administration in Gram-negative meningitis. ‖Addition of rifampicin should be considered. **Choice of a specific agent should be based on in-vitro susceptibility testing. ††Might also need to be administered by the intraventricular or intrathecal routes.

Table 4*: Antibiotics for bacterial meningitis after microorganism identification and in-vitro susceptibility testing

should depend on the local prevalence of meticillin-resistant *S aureus*; antistaphylococcal penicillins are more effective than is vancomycin for the treatment of severe *S aureus* disease, but empirical vancomycin can be used until susceptibility testing results are ready.[40]

Duration of antibiotic therapy

Antibiotics need enough time to kill all the bacteria and prevent disease recurrence, but the timescale of this process varies widely and depends on the causative bacteria, disease severity, and antimicrobial agent used. Uncomplicated meningococcal disease can be treated effectively with one intramuscular dose of ceftriaxone or oily chloramphenicol, both of which are recommended by WHO in African meningococcal meningitis epidemics.[29,41] WHO recommends at least 5 days of treatment in non-epidemic situations, in patients younger than 24 months, or if fever, coma, or convulsions last for longer than 24 h.[41] In a meta-analysis of five controlled trials investigating shorter (4–7 days) versus longer (7–14 days) antibiotic treatments for bacterial meningitis, investigators noted no difference in outcome.[41,42] In a controlled trial in 1027 children with bacterial meningitis caused by *S pneumoniae*, *H influenzae*, or *N meningitidis* in Bangladesh, Egypt, Malawi, Pakistan, and Vietnam, the investigators reported no differences in treatment failure or relapse between 5 days versus 10 days of ceftriaxone treatment.[43] Nevertheless, many authorities in high-income countries recommend at least 7 days of treatment for haemophilus and meningococcal meningitis, and 10–14 days of treatment for pneumococcal meningitis.[3,6]

New antibiotics for meningitis

The increasing prevalence of meningitis caused by resistant bacteria has led to the consideration of new antimicrobial agents for therapy, although data describing their role are generally limited to extrapolations from experimental animal models and case reports. We will limit our discussion to agents that have been assessed in patients with bacterial meningitis.

Cefepime

The fourth-generation cephalosporin cefepime has broad-range activity and greater stability against β-lactamases, including those often produced by *Pseudomonas aeruginosa,* than have agents from the preceding generation (eg, ceftriaxone and cefotaxime). Findings from experimental meningitis models and some human studies suggested that cefepime could have better CSF activity than ceftriaxone, including against penicillin-resistant *S pneumoniae*;[44,45] however, in two controlled trials of 345 children with bacterial meningitis, the investigators reported that cefepime has similar efficacy to cefotaxime and ceftriaxone.[44,45] The Infectious Diseases Society of America (IDSA) guidelines recommend cefepime as a second-line agent in the treatment of *H influenzae* meningitis, and either cefepime or ceftazidime as empirical first-line treatment in patients with post-neurosurgical meningitis.[6]

Carbapenems

Of the β-lactams, the carbapenems possess the broadest range of in-vitro activity against Gram-positive and Gram-negative bacteria. Results from studies in human beings suggest that meropenem has better CSF penetration than do imipenem and doripenem.[8,46] In four controlled trials of 448 children and 58 adults, meropenem had similar efficacy and safety to cefotaxime or ceftriaxone, making meropenem the carbapenem of choice in the treatment of bacterial meningitis.[8] The emergence of novel β-lactamases with direct carbapenem-hydrolysing activity has contributed to an increased prevalence of carbapenem-resistant Enterobacteriaceae.[47]

Fluoroquinolones

The fluoroquinolones gatifloxacin and moxifloxacin penetrate the CSF effectively and have greater in-vitro activity against Gram-positive bacteria than do their earlier counterparts (eg, ciprofloxacin). Findings from experimental meningitis models suggested their efficacy in *S pneumoniae* meningitis, including that caused by penicillin-resistant and cephalosporin-resistant strains.[48,49] Although one controlled trial suggested the fluoroquinolone trovafloxacin mesilate to be as effective as ceftriaxone, with or without the addition of vancomycin, for paediatric bacterial meningitis,[50] no clinical trials describe the use of gatifloxacin or moxifloxacin to treat bacterial meningitis in human beings. Trovafloxacin and gatifloxacin have been associated with serious hepatic toxicity and dysglycaemia, respectively, and were withdrawn from many markets.[51] The IDSA guidelines recommend moxifloxacin as an alternative to third-generation cephalosporins plus vancomycin for meningitis caused by *S pneumoniae* strains resistant to penicillin and third-generation cephalosporins,[6] although some experts recommend that this agent should not be used alone but rather should be combined with another drug (either vancomycin or a third-generation cephalosporin), because of the absence of clinical data supporting its use.

Daptomycin

Daptomycin is a cyclic lipopeptide with solely Gram-positive activity. Although it penetrates the CSF poorly, experimental models indicate that CSF bactericidal concentrations are achieved against most susceptible organisms, and daptomycin could have greater bactericidal activity than vancomycin against β-lactam-resistant bacteria.[52] Human data are limited to case reports that describe the successful use of daptomycin (6–12 mg/kg once daily), usually combined with rifampicin, for meningitis caused by meticillin-resistant *S aureus* and vancomycin-resistant *Enterococcus* spp.[53,54]

Linezolid

Linezolid is an oxazolidinone that acts only on Gram-positive bacteria. It has never been assessed in a controlled trial in patients with bacterial meningitis, although some case reports have been published;[55] linezolid penetrates the CSF well and is associated with cure rates of about 90%. Clinical studies have reported variable CSF penetration; about 50% of patients given standard doses (600 mg every 12 h) might not achieve therapeutic CSF concentrations.[56] Higher doses and CSF concentration measurements might be needed to optimise linezolid therapy for bacterial meningitis.

Tigecycline

Tigecycline is a glycycline antibiotic that is active against many Gram-positive and Gram-negative bacteria. Data about its use in bacterial meningitis are limited mainly to case reports describing tigecycline treatment for multidrug-resistant *Acinetobacter* meningitis,[57] some of which show that standard intravenous tigecycline doses produce subtherapeutic CSF concentrations.[57,58]

Adjunctive dexamethasone therapy

Experimental animal models have shown that outcome from bacterial meningitis is related to the severity of inflammation in the subarachnoid space and could potentially be improved by modulation of the inflammatory response—eg, with dexamethasone.[59] Initial trials suggested that dexamethasone reduced the risk of hearing loss in children with *H influenzae* type b meningitis.[60] Additional data extended the likely benefit to children with *S pneumoniae* meningitis if dexamethasone was given with or before the first dose of an antibiotic agent.[60] However, subsequent randomised controlled trials in Malawian and South American children did not show a benefit of dexamethasone.[61,62] A Cochrane meta-analysis published in 2010[60] showed that adjunctive dexamethasone treatment did not reduce mortality in children with bacterial meningitis, but did decrease hearing loss from 20% in the control group to 15% in corticosteroid-treated children (risk ratio [RR] 0·74, 95% CI 0·62–0·89). None of the included studies investigated children younger than 1 month (neonatal meningitis), and one randomised, but not placebo-controlled, trial did not show a benefit of dexamethasone in neonates.[63]

For adults with community-acquired bacterial meningitis, the results of a European controlled trial showed that adjunctive dexamethasone, given before or with the first dose of antibiotic therapy, was associated with a reduced risk of unfavourable outcome (15% *vs* 25%; RR 0·59, 95% CI 0·37–0·94) and a reduction in mortality (7% *vs* 15%, 0·48, 0·24–0·96).[64] This beneficial effect was most obvious in adults with pneumococcal meningitis, in whom the mortality rate decreased from 34% to 14%. However, randomised controlled trials in Malawi and Vietnam did not show that dexamethasone benefited adult patients,[65,66] although the Vietnam trial[66] did show that dexamethasone increased survival in patients with microbiologically confirmed bacterial meningitis.

Investigators of an individual patient data meta-analysis of trials published since 2000 attempted to explain the differences between individual trial results.[67] In this analysis of 2029 patients of all age groups from five trials, treatment with adjunctive dexamethasone did not significantly reduce mortality, neurological disability, or severe hearing loss in patients with bacterial meningitis. There were no significant treatment effects in any of the prespecified subgroups. A post-hoc analysis suggested that adjunctive dexamethasone treatment reduced the rate of hearing loss in survivors (odds ratio [OR] 0·77, 95% CI 0·60–0·99; p=0·04). Adjunctive dexamethasone treatment was not associated with an increased risk of adverse events.

Guidelines recommend the use of adjunctive dexamethasone in patients with suspected or proven community-acquired bacterial meningitis, but only in high-income countries.[6,68] Dexamethasone treatment should be started with or before the first dose of antibiotics. It should be given for 4 days at a dose of 0·6 mg per kg of bodyweight intravenously every day for children, and 10 mg given intravenously every 6 h for adults. A controlled study of 118 children with bacterial meningitis showed 2-day and 4-day regimens of dexamethasone to be similarly effective.[69] However, this study was underpowered, with neurological sequelae or hearing loss occurring in 1·8% and 3·8% of patients in the 2-day and 4-day regimen groups, respectively. Dexamethasone should be stopped if the patient is discovered not to have bacterial meningitis or if the bacterium causing the meningitis is a species other than *H influenzae* or *S pneumoniae*, although some experts advise that adjunctive treatment should be continued irrespective of the causative bacterium.[3] A recent study showed that adjunctive dexamethasone is widely prescribed for Dutch patients with meningococcal meningitis and is not associated with harm.[70]

Adjunctive dexamethasone therapy has been implemented on a large scale for patients with pneumococcal meningitis in some settings. In a nationwide observational cohort study in the Netherlands,[71] the drug was given in 92% of meningitis episodes during 2006–09. This observational study reported a decrease in mortality from 30% to 20% after the introduction of adjunctive dexamethasone therapy (absolute risk difference 10%, 95% CI 4–17; p=0·001).

Cognitive deficits occur often after bacterial meningitis,[72] and studies in animals have suggested that corticosteroids can aggravate learning deficiencies.[59] A follow-up of the European study in adults did not show differences in cognitive outcome between patients who received dexamethasone and those who received placebo.[73]

A potential rare complication of dexamethasone therapy in pneumococcal meningitis is delayed cerebral thrombosis, although a causal relation between this complication and dexamethasone is difficult to establish.[74] Delayed cerebral

thrombosis can occur 7–19 days after hospital admission in patients with excellent initial recovery.[74]

Studies published so far do not address two important questions: is dexamethasone effective after the first antibiotic dose; and is dexamethasone effective in patients with septic shock? In experimental pneumococcal meningitis, CSF bacterial concentrations at the start of treatment seemed to be a more important factor affecting the antimicrobial-induced inflammatory response than the time when dexamethasone therapy was started.[75] An individual patient data meta-analysis showed that dexamethasone reduced hearing loss, irrespective of whether the drug was given before or after antibiotics.[67] In patients with bacterial meningitis and severe sepsis or septic shock, the survival benefit in patients with pneumococcal meningitis who were given adjunctive dexamethasone outweighed the risks associated with high-dose steroids.[71,76]

Other adjunctive therapies

Glycerol is a hyperosmolar agent that has been used to decrease intracranial pressure. Although glycerol had no beneficial effect in experimental meningitis models,[59] a randomised clinical trial in Finland suggested that this drug might protect against sequelae in children with bacterial meningitis.[77] A randomised controlled trial of 654 children with bacterial meningitis in several South American countries showed a significant decrease in sequelae.[62] However, a randomised controlled trial of 265 Malawian adults with bacterial meningitis showed that adjuvant glycerol was harmful and increased mortality.[78] In children, the evidence is insufficient to justify routine glycerol treatment, but a randomised controlled trial of this topic is ongoing in Malawi (NCT00619203).

Despite some reported beneficial effects of monitoring and lowering of intracranial pressure in patients with bacterial meningitis,[79] when and how it should be undertaken is unclear.[80] Randomised studies of various strategies to lower intracranial pressure have not been done. Nevertheless, in patients with impending cerebral herniation, monitoring of intracranial pressure and use of osmotic diuretics to lower intracranial pressure could be considered, but outcomes are generally poor in this critically ill group of patients.[80]

Antipyretic treatments are often administered in severely ill patients, but their effect on outcome is uncertain. In a randomised controlled trial of 723 children with bacterial meningitis in Luanda, Angola, treatment with paracetamol for the first 48 h did not increase survival.[16] Active cooling leading to hypothermia has beneficial effects in animals with pneumococcal meningitis.[59] The results of a randomised clinical trial of moderate hypothermia in patients with severe bacterial meningitis are eagerly awaited (NCT00774631).

Patients with bacterial meningitis should be monitored carefully. Seizures occur frequently and the high associated mortality rate means that the threshold at which anticonvulsant therapy is started should be low.[81] Blood glucose concentrations need to be monitored and normoglycaemia achieved.[82] The goal of fluid management should be to maintain a normovolaemic state; even in patients with severe hyponatraemia, fluid maintenance therapy should be used, rather than fluid restriction.[3] Monitoring of kidney function is also important, especially in patients who develop septic shock and in those with pre-existing kidney disease. Repeat CSF analysis should only be done in patients whose condition has not responded clinically after 48 h of appropriate antimicrobial therapy.

Novel therapeutic approaches

Investigators have used experimental meningitis models to study whether outcomes can be improved by modulation of damage caused by reactive oxygen species, or by inhibition of caspase or other mediators in the inflammatory, coagulant, or complement cascades.[59] Because bacteriolytic antibiotic regimens temporarily increase the release of bacterial components, investigators have used animal studies to explore the role of non-bacteriolytic antibiotics in the treatment of bacterial meningitis.[59] In a genetic association study in patients with bacterial meningitis,[83] investigators reported that a common non-synonymous single nucleotide polymorphism in the gene for complement component 5 (*C5*) was associated with unfavourable clinical outcome. Consistent with these human data, C5a receptor-deficient mice with pneumococcal meningitis had decreased brain damage, and adjuvant treatment with C5-specific monoclonal antibodies prevented death in all wild-type mice with pneumococcal meningitis.[83]

Conclusions and future challenges

Two main therapeutic strategies exist to improve the outcome of patients with bacterial meningitis: optimisation of antimicrobial killing with antibiotics, and reduction of the inflammatory response in the subarachnoid space with adjunctive agents such as dexamethasone. Optimisation of the antibiotic effect depends on active antibiotic therapy being started early in infection, usually before the causative bacterium and its antibiotic susceptibility are known. Determination of which antibiotic agent will be most effective is becoming ever more difficult in the face of increasingly drug-resistant bacteria. Clinical data for new antibiotics for bacterial meningitis have not kept pace with the rise of resistance, and controlled trials exploring the role of these agents are urgently needed. Dexamethasone is the only accepted adjunctive therapy for the treatment of patients with bacterial meningitis, but it has shown obvious efficacy only in high-income countries. A greater understanding of disease pathogenesis and pathophysiology could explain why dexamethasone treatment benefits some patients with bacterial meningitis, but not others, and could help to identify new adjunctive

therapeutic strategies. In the near future, controlled trials are needed to assess treatment modalities such as induction of hypothermia, intracranial pressure management, and specific monoclonal antibodies. However, the greatest effect on the burden of illness due to bacterial meningitis is likely to be achieved through widespread use of vaccinations.

Contributors

All authors contributed to writing and editing of the review, and all authors approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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