Strategies and New Developments in the Management of Bacterial Meningitis

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- Bacterial meningitis • Cerebrospinal fluid
- Antimicrobial therapy • Blood-brain barrier
- Antimicrobial resistance

Despite significant advances in the management of bacterial meningitis over the past few decades, the disease continues to have a high mortality rate, with long-term neurologic sequelae developing in many survivors.[1–3] Childhood immunization programs have proved effective in prevention,[4] with declines in the incidence of bacterial meningitis caused by *Haemophilus influenzae* type b and in invasive pneumococcal disease.[5,6] This changing epidemiology and the emergence of resistant organisms present continued challenges to therapy.[7,8] Recent retrospective reviews suggested that despite the widespread decline in invasive pneumococcal disease after use of the heptavalent pneumococcal conjugate vaccine, there is emergence of cases of pneumococcal meningitis caused by serotype strains that are not in the vaccine.[9,10] These challenges drive the need for continuing research and development of new strategies for the management of this devastating disease.

Success in the treatment of patients with bacterial meningitis and the development of improved strategies for disease management rely on knowledge of key pharmacologic principles for use of antimicrobial agents that are efficacious in the unique environment of the cerebrospinal fluid (CSF), including penetration of the drug across the blood-brain barrier (BBB), activity of the drug in purulent CSF, and the intrinsic pharmacodynamic properties of the drug.[11] Our understanding of the efficacy of antimicrobial agents in bacterial meningitis relies largely on their use in experimental animal models, particularly the rabbit model, which uses an intracisternal method of organism inoculation and sampling of CSF.[1,12] In this article, we review the principles of use of

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antimicrobial agents in the therapy of bacterial meningitis and summarize recent experimental and clinical data in the use of new antimicrobial agents.

PRINCIPLES OF ANTIMICROBIAL THERAPY

CSF Penetration

The penetration of antimicrobials across the BBB and into the CSF is the first determinant in the ability of the drug to treat bacterial meningitis effectively. The environment of the CSF is unique, and pharmacokinetic parameters are different in this compartment than in other areas of the body. Antimicrobial agents are generally not significantly metabolized in the CSF, and concentrations of most drugs primarily depend on penetration and elimination through the BBB.[13]

The microanatomy of the central nervous system (CNS) contributes to the distinct nature of the CSF environment. The presence of tight junctions and the absence of intracytoplasmic pinocytic vesicles in the microvascular endothelium of the cerebral capillaries limit the amount of drug transport into the subarachnoid space. An active transport system in the choroid plexus also eliminates compounds (eg, penicillins, cephalosporins, aminoglycosides, and fluoroquinolones) from the CSF and into the blood. A different active transport system that is present in the cerebral capillaries transports penicillins and cephalosporins from the blood to the CSF, although its low drug affinity and capacity limit its ability to transport significant drug concentrations into the CSF.[14,15]

In inflamed meninges, inflammatory cytokines act to damage and separate the tight junctions and increase the number of pinocytotic vesicles in the endothelial cells of the BBB, which enhances drug entry into the CSF.[16] These inflammatory cytokines also inhibit drug elimination by the choroid plexus system, which leads to further accumulation of agents in the CSF. These mechanisms are most important in the penetration of antimicrobial agents, such as vancomycin and β-lactams, that would otherwise not achieve adequate CSF concentrations as a result of dependence on entry through tight junctions.[13] Agents that reduce meningeal inflammation, such as dexamethasone, have been shown to decrease drug permeability into CSF in experimental animal models.[17–19] As meningeal inflammation subsides during treatment of meningitis, antimicrobial entry also decreases, indicating that appropriate antimicrobial dosages should be sustained throughout the course of therapy of meningitis to maintain adequate CSF concentrations.[1]

Intrinsic drug characteristics that determine CSF penetration are as follows:[11,14,20]

1. Lipid solubility. The ability of lipophilic agents, such as the fluoroquinolones, chloramphenicol, rifampin and sulfonamides, to enter the CSF via passive diffusion down a concentration gradient allows them to reach peak CSF concentrations more rapidly, maintain adequate CSF concentrations, and reach CSF half-lives similar to those in serum, regardless of the presence or absence of meningeal inflammation. Hydrophilic agents, such as β-lactams and vancomycin, have poor penetration and delayed onset of peak CSF concentrations because of their dependence on the opening of tight junctions for entry.
2. Molecular weight. The low molecular weight and simple structure of some drugs, such as the fluoroquinolones and rifampin, correlate with improved CSF penetration compared with larger compounds with more complex structures, such as vancomycin.
3. Ionization. In bacterial meningitis, the pH of CSF is lower than that of plasma, and antibiotics with high ionization have poor CSF penetration. β-lactam antibiotics, which are weak acids and highly ionized in the physiologic pH of plasma, have

poor penetration into the CSF and tend to pass from the CSF into the plasma instead of in the reverse direction.
4. Protein binding. Only unbound fractions of antimicrobials enter the CSF; a high degree of protein binding in the serum (eg, with ceftriaxone) limits the degree of CSF penetration.

The percent penetration of individual antimicrobial agents into CSF can be assessed in several ways. Because the concentration time curve of drugs in the CSF lags behind that in the serum, assessment of penetration by simultaneous sampling of serum and CSF concentrations can yield inaccurate results.[21] The ratio of the area under the concentration curve in the CSF to that in serum is a more accurate assessment than measuring peak concentrations in serum and CSF; however, this method is not feasible in human studies because it requires multiple sampling of the CSF and serum.[13] Most available data use concentration ratios, but this method should be considered to provide only an approximation of percent penetration because of differences in drug delivery, timing of sampling, and underlying differences among patients.

Activity in Purulent CSF

The activity of the drugs in the purulent CSF of bacterial meningitis is a second determinant of its efficacy. The following factors contribute to drug activity:[1,11,12,20]

1. CSF pH. Accumulation of lactate in bacterial meningitis decreases CSF pH, which inhibits the activity of certain drugs, such as the aminoglycosides. Clarithromycin, which in one experimental study exhibited good in vitro activity against a pneumococcal strain, was found to have no bactericidal activity in the CSF of test animals, possibly because of a substantial increase in the minimal bactericidal concentration (MBC) of clarithromycin in the acidic environment of CSF.[22]
2. CSF protein concentration. Elevated protein concentrations in purulent CSF may diminish the amount of free drug available for microbial killing.
3. Bacterial growth. A slower bacterial generation time in CSF compared with maximal growth rates in vitro may reduce the bactericidal effects of drugs such as β-lactams, which rely on bacterial growth for optimal bactericidal activity.
4. Metabolism. Some antimicrobial agents undergo metabolism to compounds with different antimicrobial activity. For example, cephalothin is converted in vivo to desacetylcephalothin, which is less active than the parent compound. In contrast, cefotaxime is metabolized in vivo to desacetylcefotaxime, which has equal activity compared with its parent compound.
5. Synergy and antagonism. Some drug combinations may act synergistically when coadministered, such as penicillin or ampicillin with gentamicin in *Listeria monocytogenes* meningitis, ampicillin plus mecillinam in *Escherichia coli* meningitis, and ampicillin plus gentamicin against *Streptococcus agalactiae*. Recent experimental studies also found synergy between levofloxacin and either ceftriaxone or cefotaxime in a rabbit model of pneumococcal meningitis.[23,24] On the other hand, antagonism has been demonstrated when bactericidal agents are coadministered with a bacteriostatic agent, such as chloramphenicol with either penicillin or gentamicin.
6. Inoculum effect. High bacterial loads can be found in the CSF in bacterial meningitis, with bacterial concentrations of 10^8 CFU/mL or more. In this environment, the minimal inhibitory concentration (MIC) of some antimicrobial agents against specific micro-organisms may increase dramatically, a phenomenon called the inoculum effect.[25,26]

Mode of Administration

The third determinant of success for an antimicrobial agent in bacterial meningitis is the mode of administration of the drug, whether by intermittent or continuous intravenous administration.[20] Although the standard clinical practice is intermittent administration, which leads to higher peak CSF concentrations, this method may not maintain concentrations above the MBC for the entire dosing interval. On the other hand, continuous infusion allows maintenance above the MBC during nearly 100% of the dosing interval, although a lower peak CSF concentration is attained.[11] The mode of administration has been a concept of considerable debate, but a recent meta-analysis of randomized controlled trials involving severe infections mainly outside the CNS showed that fewer clinical failures were seen in infections treated with continuous intravenous infusion of antibiotics that act by time-dependent killing (eg, β-lactams) and even with aminoglycosides that exhibit concentration-dependent killing.[27]

Antimicrobial Pharmacodynamics in CSF

The fourth and final determinant of response to antimicrobial therapy in bacterial meningitis is pharmacodynamics, which is concerned with the antimicrobial effect of drug concentrations in a particular site of infection over time. Knowledge of the pharmacodynamic properties of antimicrobials allows for appropriate optimization of bactericidal drug concentrations.[14] Bacterial killing is particularly important in the CSF, in which there is a decreased immune response from relatively lower concentrations of antibody and complement and inefficient phagocytosis.[12]

Antibiotics may exhibit ether time-dependent or concentration-dependent killing. Time-dependent antimicrobial activity, demonstrated by the β-lactam antibiotics and vancomycin, depends on the time that the drug concentration in CSF is above the MBC (T > MBC). An experimental study of cephalosporin-resistant pneumococcal meningitis showed that the T > MBC was the most important single determinant of ceftriaxone efficacy and correlated best with the bacterial kill rate;[28] a direct linear relationship was found between T > MBC and the bacterial killing rate. Aminoglycosides and fluoroquinolones exhibit concentration-dependent killing,[29,30] although fluoroquinolones, particularly trovafloxacin and gatifloxacin, have been shown to have features of time-dependent killing, in which the T > MBC was also considered a factor in bacterial killing.[31,32] The efficacy of concentration-dependent killing depends on attaining high peak CSF concentrations and a prolonged recovery period, or a postantibiotic effect, once the antibiotic concentration falls to below the MIC.

SELECTED ANTIMICROBIAL AGENTS IN THE TREATMENT OF BACTERIAL MENINGITIS

Most clinical trials of antimicrobial agents in patients with bacterial meningitis have compared new agents with standard therapy, although most of these standard agents have not been completely studied themselves, and no placebo-controlled studies exist in humans. Much of what we know is based on studies in experimental animal models, which have been used to develop guidelines for treatment recommendations (**Table 1**) and to determine optimal dosages of agents that achieve adequate CSF concentrations for bactericidal activity (**Table 2**).[33] The most commonly used class of antimicrobial agents in the treatment of bacterial meningitis have been the β-lactams, especially penicillin G and ampicillin, which have proved to be effective against a wide variety of meningeal pathogens. These agents are well tolerated and generally attain CSF concentrations well above the MIC of sensitive pathogens when administered at high doses. The emergence of penicillin resistance in specific meningeal pathogens has led to the use of other β-lactam agents, including third-generation

Table 1
Recommendations for specific antimicrobial therapy in bacterial meningitis based on isolated pathogen and in vitro susceptibility testing

Microorganism	Standard Therapy	Alternative Therapies
Streptococcus pneumoniae		
Penicillin MIC <0.1 μg/mL	Penicillin G or ampicillin	Third-generation cephalosporin;[a] chloramphenicol
Penicillin MIC 0.1-1.0 μg/mL[b]	Third-generation cephalosporin[a]	Cefepime; meropenem
Penicillin MIC ≥2.0 μg/mL; or cefotaxime or ceftriaxone MIC ≥1.0 μg/mL	Vancomycin + a third-generation cephalosporin[a,c]	Fluoroquinolone[d]
Neisseria meningitidis		
Penicillin MIC <0.1 μg/mL	Penicillin G or ampicillin	Third-generation cephalosporin;[a] chloramphenicol
Penicillin MIC 0.1–1.0 μg/mL	Third-generation cephalosporin[a]	Chloramphenicol; fluoroquinolone; meropenem
Listeria monocytogenes	Ampicillin or penicillin G[e]	Trimethoprim-sulfamethoxazole
Streptococcus agalactiae	Ampicillin or penicillin G[e]	Third-generation cephalosporin[a]
Escherichia coli and other Enterobacteriaceae[g]	Third-generation cephalosporin	Aztreonam; fluoroquinolone; meropenem; trimethoprim-sulfamethoxazole; ampicillin
Pseudomonas aeruginosa[g]	Cefepime[e] or ceftazidime[e]	Aztreonam;[e] ciprofloxacin;[e] meropenem[e]
Haemophilus influenzae		
β-lactamase-negative	Ampicillin	Third-generation cephalosporin;[a] cefepime; chloramphenicol, fluoroquinolone
β-lactamase-positive	Third-generation cephalosporin[a]	Cefepime; chloramphenicol, fluoroquinolone
Staphylococcus aureus		
Methicillin-susceptible	Nafcillin or oxacillin	Vancomycin; meropenem; linezolid; daptomycin
Methicillin-resistant	Vancomycin[f]	Trimethoprim-sulfamethoxazole; linezolid; daptomycin
Staphylococcus epidermidis	Vancomycin[f]	Linezolid

[a] Ceftriaxone or cefotaxime.
[b] Ceftriaxone/cefotaxime susceptible isolates.
[c] Consider addition of rifampin if ceftriaxone MIC is > 2 μg/mL.
[d] Moxifloxacin. No clinical data available; if used, many authorities would combine with vancomycin or a third-generation cephalosporin (eg, cefotaxime or ceftriaxone).
[e] Addition of an aminoglycoside should be considered.
[f] Consider addition of rifampin.
[g] Choice of a specific antimicrobial agent must be guided by in vitro susceptibility testing.
Data from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267–84.

Table 2
Recommended dosages of antimicrobial therapy in adult patients with bacterial meningitis with normal renal and hepatic function

Antimicrobial Agent	Total Daily Dose (Dosing Interval in Hours)
Amikacin[a]	15 mg/kg (8)
Ampicillin	12 g (4)
Aztreonam	6–8 g (6–8)
Cefepime	6 g (8)
Cefotaxime	8–12 g (4–6)
Ceftazidime	6 g (8)
Ceftriaxone	4 g (12–24)
Chloramphenicol	4–6 g (6)[b]
Ciprofloxacin	800–1200 mg (8–12)
Gentamicin[a]	5 mg/kg (8)
Meropenem	6 g (8)
Moxifloxacin	400 mg (24)[c]
Nafcillin	9–12 g (4)
Oxacillin	9–12 g (4)
Penicillin G	24 mU (4)
Rifampin	600 mg (24)
Tobramycin[a]	5 mg/kg (8)
Trimethoprim-sulfamethoxazole[d]	10–20 mg/kg (6–12)
Vancomycin[e]	30–60 mg/kg (8–12)

[a] Need to monitor peak and trough serum concentrations.
[b] Higher dose recommended for patients with pneumococcal meningitis.
[c] No data on optimal dosage needed in patients with bacterial meningitis.
[d] Dosage based on trimethoprim component.
[e] Maintain serum trough concentrations of 15–20 μg/mL; one study administered vancomycin as a continuous infusion at a total daily dose of 60 mg/kg (see text for details).[64]

Data from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267–84.

cephalosporins and carbapenems. Some organisms also have been difficult to eradicate with standard therapy, necessitating use of alternative agents in selected patients. The following sections review antimicrobial agents that have been studied in experimental animals and patients with bacterial meningitis, with a focus on newer drugs.

Cephalosporins

The cephalosporins, specifically third-generation agents, are integral in the treatment of bacterial meningitis and are the standard of therapy for meningitis caused by pneumococcal and meningococcal strains previously defined as being of intermediate susceptibility to penicillin (MIC 0.1–1 μg/mL).[33] Past clinical trials have clearly demonstrated the superiority of third-generation cephalosporins to chloramphenicol and second-generation cephalosporins (ie, cefuroxime) in the treatment of bacterial meningitis.[34,35] A recent noninferiority trial of 308 patients with confirmed epidemic meningococcal meningitis in Africa supported the use of ceftriaxone as an alternative to intramuscular oily chloramphenicol for short-course therapy.[36] Ceftazidime is a third-generation cephalosporin effective in the therapy of *Pseudomonas aeruginosa*

meningitis[37,38] and experimental *Klebsiella pneumoniae* meningitis.[39] A recent study of 25 cases of culture-proven *P aeruginosa* meningitis in Taiwan determined a ceftazidime susceptibility rate of 91.7%.[40]

Cefepime is a fourth-generation cephalosporin with a broad antimicrobial spectrum that was found in early experimental animal models to be effective against a variety of meningeal pathogens, including *S pneumoniae, Streptococcus agalactiae*, *E coli*, *K pneumoniae,* and *P aeruginosa*.[41] It also has been used successfully in the treatment of meningitis caused by *Enterobacter aerogenes*.[42] Its efficacy against penicillin-resistant *S pneumoniae* was previously elucidated in two experimental studies using the rabbit model. One of these studies showed that the superior bacterial killing of cefepime compared with ceftriaxone was statistically significant in vivo despite similar antimicrobial activity in vitro. Cefepime monotherapy was also proven to be as effective as the combination of vancomycin plus ceftriaxone against penicillin-resistant *S pneumoniae* isolates with induced fluoroquinolone resistance.[43] Cefepime had similar bacterial killing rates to that of vancomycin and ceftriaxone in vivo, although the fluoroquinolone-resistant strain was killed more slowly by cefepime and ceftriaxone compared with the parent fluoroquinolone-susceptible strain.[44]

A study in hospitalized patients that compared cefepime with ceftriaxone against *S pneumoniae* verified the superior pharmacodynamics of cefepime by determining the pharmacodynamic profiles of ceftriaxone and cefepime in the CSF and serum of hospitalized patients with external ventricular drains.[45] The probability of ceftriaxone achieving 50% and 100% T > MIC in CSF was less than 80%, whereas cefepime had a more than 90% and 82% probability of achieving 50% and 100% T > MIC, respectively, in the CSF against *S pneumoniae*. Although ceftriaxone had a low probability of providing adequate exposure in CSF for *S pneumoniae* strains with MIC values more than 0.03 μg/mL, cefepime had a high probability of ensuring adequate exposure for MIC values up to 0.5 μg/mL. These data are favorable for cefepime, although the model was derived from noninflamed meninges in patients with hydrocephalus. In the setting of pediatric meningitis in Latin America, cefepime was shown to be clinically effective and to have comparable activity to ceftriaxone and cefotaxime,[46] which indicates that cefepime is an important therapeutic option in the empiric treatment of pediatric bacterial meningitis.

Carbapenems

The carbapenems that have been studied for use in bacterial meningitis are imipenem, ertapenem, and meropenem. Imipenem has been shown to be effective in pneumococcal meningitis caused by penicillin- and cephalosporin-resistant strains; however, given its potential for seizure activity (up to 33% in one study),[47] it is not recommended for use in therapy for bacterial meningitis.[33] Ertapenem lacks in vitro activity against *P aeruginosa* and *Enterococcus* species, although it has a broad antimicrobial spectrum and was found to be effective in an experimental study of pneumococcal meningitis in rabbits caused by penicillin-sensitive (MIC 0.03 μg/mL) and penicillin-resistant (MIC 0.5 μg/mL) strains.[48,49] During the entire treatment period, ertapenem achieved CSF concentrations above the MICs of both strains, denoting sufficient penetration into inflamed meninges, and was successful in sterilizing the CSF in animals with infection caused by penicillin-sensitive and penicillin-resistant strains.

Meropenem has been the most studied carbapenem in patients with bacterial meningitis.[33] It is less neurotoxic and has a lower risk of inducing seizures compared with imipenem, likely because of the less basic C-2 side chain of its chemical structure.[50] Four randomized clinical trials in adults and children compared meropenem to cefotaxime and ceftriaxone in the treatment of bacterial meningitis and

demonstrated that meropenem was clinically and microbiologically comparable to cefotaxime and ceftriaxone. Meropenem dosages of 40 mg/kg every 8 hours were used, and rapid CSF sterilization was achieved in all patients in all four study groups (18–36 hours in most patients). Clinical cure was seen in 97% to 100% of patients, and no seizure activity was thought to be related to therapy.[51–53] A recent experimental study in guinea pigs also found a comparable efficacy of meropenem compared with ceftazidime in the treatment of *P aeruginosa* meningitis.[54]

Although the clinical data for meropenem in the treatment of bacterial meningitis are favorable, reports of meropenem resistance in cephalosporin-resistant *S pneumoniae* have become a growing concern,[55] and recent experimental studies have further elucidated the activity of meropenem in penicillin- and cephalosporin-resistant pneumococcal meningitis. A study in rabbits evaluated the therapeutic efficacy of meropenem monotherapy compared with the combination of meropenem plus vancomycin caused by a highly penicillin- and cephalosporin-resistant strain of *S pneumoniae*. In that study, intermediate susceptibility to meropenem was found (MIC 0.5 μg/mL in one strain). Despite administration of meropenem at high doses (125 mg/kg) to maintain adequate CSF concentrations, meropenem monotherapy showed only a bacteriostatic effect on the study strain, with regrowth of the isolate at 24 hours. The addition of vancomycin to meropenem showed a statistically significant improvement in bacteriologic response and was comparable to therapy with ceftriaxone and vancomycin, although synergy was not found.[56] Another recent experimental study used two different animals—the rabbit and guinea pig—to evaluate meropenem therapy in meningitis caused by cephalosporin-susceptible and cephalosporin-resistant *S pneumoniae* strains. There was excellent bactericidal activity against the cephalosporin-susceptible strain in both animal species and against the cephalosporin-resistant strain in guinea pigs, but there was therapeutic failure in the rabbits inoculated with the cephalosporin-resistant strain.[57] That result suggested that meropenem may not be useful as monotherapy in the treatment of pneumococcal meningitis caused by highly penicillin- and cephalosporin-resistant strains.

Glycopeptides

Vancomycin has become important in the treatment of bacterial meningitis in the past decade, particularly as a result of the rise of pneumococcal resistance to penicillin. It is recommended that the empiric therapy of bacterial meningitis in all patients 1 month of age and older include vancomycin combined with a third-generation cephalosporin to treat for the possibility of pneumococcal meningitis caused by highly penicillin- and cephalosporin-resistant strains, pending organism identification and in vitro susceptibility testing.[33] Vancomycin has been found to be synergistic when combined with ceftriaxone in cephalosporin-resistant pneumococcal meningitis[58] and when combined with gentamicin against penicillin-resistant pneumococci in vitro and in a rabbit model of meningitis.[59] Important concerns regarding the use of vancomycin are its diminished CSF penetration in the presence of dexamethasone and the emergence of vancomycin tolerance in some *S pneumoniae* isolates.

Past experimental studies of vancomycin use in pneumococcal meningitis have demonstrated the significantly lower CSF concentrations of vancomycin after administration with dexamethasone compared with vancomycin administration alone.[17,18,60] In humans, two published studies demonstrated conflicting results. The first study of 11 adults with pneumococcal meningitis used vancomycin at a dose of 15 mg/kg/d and revealed low to undetectable CSF vancomycin concentrations after concomitant administration of dexamethasone.[61] In the second study, children with bacterial meningitis were given vancomycin at a dose of 60 mg/kg/d with ceftriaxone and

dexamethasone, which resulted in acceptable CSF concentrations of vancomycin.[62] The higher dose administered in the second study may have contributed to the favorable results, as was demonstrated by an experimental study of penicillin- and cephalosporin-resistant pneumococci in rabbits, in which regimens of 20 mg/kg/d and 40 mg/kg/d of vancomycin plus dexamethasone were compared.[63] Rates of bacterial clearance from CSF were similar with both dosage regimens, but the coadministration of dexamethasone significantly reduced the CSF penetration of vancomycin and bacterial clearance in animals receiving the 20 mg/kg dose. For animals receiving the 40 mg/kg dose of vancomycin, therapeutic peak CSF concentrations of vancomycin were attained even with use of adjunctive dexamethasone, which suggested that the effects of steroids on antimicrobial penetration may be circumvented by using larger vancomycin doses. A strong positive linear correlation between serum and CSF concentrations of vancomycin was also demonstrated in a recent prospective multicenter observational study of 14 adults with suspected pneumococcal meningitis who received vancomycin (in a continuous infusion of 60 mg/kg/d after a loading dose of 15 mg/kg), combined with cefotaxime and dexamethasone. The mean serum and CSF vancomycin concentrations were 25.2 μg/mL and 7.9 μg/mL, respectively, and follow-up CSF analysis revealed negative bacterial culture results and marked improvement in CSF parameters in all patients. These findings suggest that higher vancomycin dosages may overcome diminished vancomycin CSF penetration associated with dexamethasone administration.[64]

Another concern with the use of vancomycin is the emergence of a genetic trait in pneumococci called tolerance, which is the ability of the bacteria to evade killing through loss of antimicrobial-induced autolysin activity. Tolerance reduces the rate of death on exposure to an antimicrobial agent and allows for a resumption of growth after its removal, effectively changing the antimicrobial activity from bactericidal to bacteriostatic, with attenuated killing at the defined MIC for the given isolate. Once thought to be sporadic, it is currently believed to be present in a large number of pneumococcal serotypes.[65,66] In 1998, a case of vancomycin-tolerant *S pneumoniae* was reported in a child who developed recrudescent meningitis 8 days after receiving a 10-day course of parenteral vancomycin and cefotaxime.[67] In a recent study, *S pneumoniae* strains from 215 nasopharyngeal swabs of healthy vaccinated infants and 113 isolates from patients with pneumococcal meningitis were recently tested for vancomycin tolerance.[66] Tolerance to vancomycin was detected in 3.7% of the nasopharyngeal swabs and 10.6% of the invasive isolates. The patients with meningitis caused by the identified tolerant isolates had a worse estimated 30-day survival than patients with meningitis caused by nontolerant isolates (49% versus 86%; $P = .048$).

Two other glycopeptides have been studied for use in bacterial meningitis. Oritavancin, a novel semisynthetic glycopeptide with long half-life and a mechanism of action resembling that of vancomycin, has in vitro activity against vancomycin-resistant microbes and has been studied in experimental animal models of pneumococcal meningitis. One study in animals with penicillin-susceptible *S pneumoniae* meningitis showed that despite low CSF penetration (1%–5%), oritavancin exhibited similar bacterial killing rates compared with ceftriaxone. It also had a low MIC and MBC against the test pneumococcal isolate (0.015 and 0.03 μg/mL, respectively) and was found to influence the release of a lower amount of proinflammatory bacterial compounds (lipoteichoic and teichoic acids) in vitro than ceftriaxone, although it had comparable effects in vivo.[68] Another study in rabbits examined the treatment of cephalosporin-resistant pneumococci by oritavancin alone and in combination with ceftriaxone. There was a rapid decrease in bacterial concentrations at 2 hours (2 log CFU/mL), and the drug was bactericidal at 6 hours (mean reduction 3.5 log CFU/mL). This activity was

improved by addition of ceftriaxone (mean reduction 3.99 log CFU/mL), although not statistically significant, possibly because of the rapid decrease in bacterial concentrations with combination therapy. The bacterial killing rate in most cases was not affected by dexamethasone administration, and there were no therapeutic failures in all study animals.[69] These data are encouraging, although no studies in humans have been performed to define the safety and efficacy of oritavancin in patients with bacterial meningitis.

Teicoplanin, another glycopeptide first discovered in 1978, has been studied for use in bacterial meningitis. When used alone in experimental treatment of pneumococcal meningitis, teicoplanin resulted in effective bacterial killing and bactericidal activity at 24 hours without evidence of therapeutic failures. The addition of dexamethasone did not alter this result, despite a significant reduction in the penetration of teicoplanin into CSF (from 2.31% to 0.71%). Ceftriaxone combined with teicoplanin did not show a significant improvement in bacterial killing despite in vitro synergy.[70] Teicoplanin has been used in the treatment of meningitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA), which has emerged as an important cause of nosocomial CNS infection. It has been reported to be effective in the treatment of staphylococcal meningitis in neonates after intrathecal administration and via intravenous administration in the treatment of six cases of culture-proven MRSA meningitis.[71,72] An experimental study in rabbits with MRSA meningitis compared teicoplanin with vancomycin and showed comparable antimicrobial activity of each, with similar CSF bacterial counts at 28 and 40 hours after inoculation.[73]

Rifampin

Most studies of rifampin in bacterial meningitis investigated its use in combination therapy with other agents, most commonly a cephalosporin and vancomycin, because of the rapid emergence of bacterial resistance that is seen with rifampin monotherapy. One study of a cephalosporin-resistant *S pneumoniae* strain, using the CSF of children treated with a combination of ceftriaxone and rifampin, reported that the addition of rifampin to ceftriaxone enhanced the CSF activity against the isolate.[62] This result was also seen in an earlier experimental study of penicillin- and cephalosporin-resistant pneumococcal meningitis in rabbits, in which prompt bacteriologic cure occurred when rifampin was used with ceftriaxone, with or without the addition of dexamethasone therapy.[17] This study also demonstrated that rifampin concentrations in the CSF were unaffected by dexamethasone administration, an observation further elucidated by a later experimental study,[60] in which rifampin was studied in combination with vancomycin in the treatment of penicillin-resistant pneumococcal meningitis. The interference of dexamethasone on the CSF vancomycin concentrations was less pronounced when rifampin was used simultaneously, likely a result of enhanced dexamethasone metabolism in the presence of rifampin.

Two recent experimental studies in rabbits of penicillin- and cephalosporin-resistant *S pneumoniae* meningitis have compared the use of ceftriaxone and rifampin combination therapy to combination regimens that include vancomycin. In both studies, the addition of rifampin to ceftriaxone was comparable in efficacy to ceftriaxone and vancomycin, one showing it to be equally effective[74] and the other showing it to be superior.[75] The drug combination consisting of vancomycin, rifampin, and ceftriaxone had similar therapeutic efficacy to the combined ceftriaxone and rifampin regimen.[75] Compared to ceftriaxone, rifampin has been found to release less proinflammatory cell wall products from *S pneumoniae* in vitro and a lower amount of reactive oxygen species produced by CSF phagocytes and endothelial cells. This correlated with

attenuated neuronal damage and a reduction in mortality in two animal models of pneumococcal meningitis.[76,77]

Fluoroquinolones

The fluoroquinolones have excellent in vitro activity against many of the meningeal pathogens and good penetration into CSF and have been used successfully in patients with gram-negative meningitis.[78–80] Trovafloxacin is one agent that showed great promise in a multicenter, randomized trial in children with bacterial meningitis, in which no significant differences between trovafloxacin and ceftriaxone, with or without vancomycin, were detected in terms of clinical success at 5 to 7 weeks after treatment (79% versus 81%), deaths (2% versus 3%), seizures (22% versus 21%), or severe sequelae (14% versus 14%).[81] Despite these favorable results, however, reports of liver toxicity have largely precluded the use of trovafloxacin. Newer fluoroquinolones, including gemifloxacin, moxifloxacin, gatifloxacin, and garenoxacin, have been developed and show excellent in vitro activity against gram-positive bacteria. These drugs, along with clinafloxacin, have been studied in experimental cases of pneumococcal meningitis with mostly efficacious results.[58,82–92]

Moxifloxacin is a promising new fluoroquinolone that was recently found in experimental rabbit models to have similar antibacterial activity to the combination of ampicillin plus gentamicin in the treatment of meningitis caused by *Listeria monocytogenes*.[93] It has also been evaluated in experimental *E coli* meningitis to be at least as effective as ceftriaxone and more effective than meropenem; it was found to have excellent CSF penetration (50%–85%).[30] A recent study in healthy humans evaluated the CSF penetration of moxifloxacin after a single oral dose of 400 mg and found good penetration that would attain CSF concentrations to achieve a satisfactory bactericidal effect against penicillin-resistant *S pneumoniae*.[94] Given the previous experimental data that demonstrated satisfactory penetration of moxifloxacin through inflamed meninges, the authors hypothesized that moxifloxacin concentrations may be even higher in the CSF of patients with meningitis.

Three experimental studies in rabbits demonstrated a synergy between fluoroquinolones and other antibiotics commonly used in bacterial meningitis. In the first study, the combination of meropenem and levofloxacin was shown to increase the efficacy of levofloxacin against penicillin-resistant pneumococcal strains in vitro, reaching higher efficacy than the standard regimen of ceftriaxone and vancomycin.[95] The second study evaluated cefotaxime and levofloxacin combined and found higher bactericidal activity of combination therapy compared with monotherapy, the efficacy of which was twice that of standard ceftriaxone and vancomycin, and confirmed synergy between the two antimicrobials. The combination almost completely diminished levofloxacin-induced resistance of the test train, with a twofold increase in the MIC.[24] The third study examined the effect of ceftriaxone and levofloxacin combined and found similar synergy with the combination regimen and the reduction of levofloxacin resistance in the pneumococcal strain. Specifically, it was determined that ceftriaxone prevented the emergence of mutations in the pneumococcal genome that contributed to a high-level resistance (MIC 64 μg/mL) to levofloxacin in the test strain.[23]

Daptomycin

Daptomycin, a cyclic lipopeptide antimicrobial agent, has potent bactericidal activity against multidrug-resistant gram-positive organisms.[96] Its clinical use has largely been in complicated skin and soft tissue infections, and there is little clinical experience with its use in bacterial meningitis. In a rabbit model of meningitis caused by

penicillin- and quinolone-resistant pneumococci,[97] there was a 6% penetration of daptomycin into CSF, a concentration sufficient to produce highly bactericidal concentrations (CSF concentration/MIC ratios between 86 and 53). Daptomycin had comparable efficacy and more rapid bacterial killing when compared with cefotaxime and levofloxacin combined but had superior efficacy compared with the combination of ceftriaxone and vancomycin. In a rabbit model of methicillin-sensitive *S aureus* meningitis, daptomycin was also found to be superior to vancomycin in efficacy in vivo and in time-killing assays in vitro.[98] There was rapid sterilization of the CSF in both models by daptomycin within 4 to 6 hours of initiation of therapy.

Two recent studies have described the nonbacteriolytic activity of daptomycin in the therapy of meningitis, which may be beneficial in preventing the release of proinflammatory mediators from cell wall components after bacterial lysis. The first study compared the measured amount of [^{3}H]choline, a main component of the proinflammatory mediators teichoic acid and lipoteichoic acid, in the CSF of rabbits with penicillin-resistant pneumococcal meningitis after treatment with ceftriaxone and daptomycin.[99] There were drastic increases in [^{3}H]choline concentrations and observed cell wall morphologic alterations via electron microscopy after ceftriaxone administration and only mild elevations in [^{3}H]choline concentrations with no morphologic changes in pneumococcal cell walls after daptomycin administration. The second study examined the effects of ceftriaxone and daptomycin therapy on cortical brain damage in infant rats with pneumococcal meningitis.[100] Only the animals treated with ceftriaxone had cortical brain damage (0.26%–7.26% in 7 of 28 animals) as evidenced by areas of cortical necrosis upon histologic analysis of brain sections of sacrificed animals 40 hours after therapy. None of the 30 animals given daptomycin had evidence of cortical damage on histologic analysis.

Recently, a case report demonstrated the success of daptomycin (combined with rifampin) in the treatment of MRSA meningitis.[101] There was clinical improvement of the patient with eventual discharge from the hospital and no residual neurologic deficits after a treatment course of 42 days. These results supported the potential of daptomycin in patients with bacterial meningitis, although more data are needed.

Linezolid

Linezolid is a novel antimicrobial of the oxazolidinone class with in vitro activity against numerous gram-positive organisms,[102] and it has been used in isolated cases in patients with bacterial meningitis. A recent review of documented CNS infections noted cure or clinical improvement in 90% of cases identified. In these cases, linezolid therapy, dosed at 600 mg twice daily as monotherapy or in a combination regimen, was started after initial therapeutic regimens failed or were associated with adverse effects.[103] Linezolid was reported to be effective in meningitis caused by penicillin-nonsusceptible *S pneumoniae*, vancomycin-resistant *Enterococcus* species, methicillin-resistant *Staphylococcus epidermidis*, MRSA, and heteroresistant vancomycin-intermediate *S aureus.* To date, no clinical trials have compared linezolid with standard therapy for bacterial meningitis, although an experimental study in rabbits with meningitis caused by penicillin-sensitive and penicillin-resistant pneumococci showed inferior killing rates of linezolid compared with ceftriaxone plus vancomycin despite good CSF penetration (38% $\pm$ 4%).[104] There was a more pronounced antibacterial activity of the agent against penicillin-resistant pneumococci than against penicillin-sensitive strains.

Telavancin

A semisynthetic derivative of vancomycin, telavancin, is an investigational lipoglycopeptide antimicrobial with bactericidal activity against gram-positive bacteria and a favorable spectrum of activity against drug-resistant streptococci, enterococci, and staphylococci. It has an MIC two to eight times lower than vancomycin for these organisms.[105] Clinical experience with the use of telavancin in patients with meningitis has not yet been reported, but an experimental study in rabbits examined its use in meningitis caused by penicillin-resistant pneumococci and methicillin-sensitive *S aureus*. CSF concentrations of telavancin remained above the MIC for both strains, leading to CSF/MIC ratios from 30 to 63 for the pneumococcal strain and 0.9 to 1.9 for the staphylococcal strain. Penetration was 2% through inflamed meninges and less than 1% through noninflamed meninges. The combination of ceftriaxone and vancomycin proved to be less efficacious than telavancin for the pneumococcal strain. Although telavancin was slightly superior to vancomycin alone against the staphylococcal strain, this difference was not statistically significant.[106]

SUMMARY

Bacterial meningitis is a life-threatening disease and is associated with significant long-term sequelae in surviving patients. Success in its treatment relies on knowledge of the fundamental principles of antimicrobial therapy in the unique environment of the CSF, including CSF penetration, activity in purulent CSF, mode of administration of the drug, and pharmacodynamic properties within the CSF. Although promising results have been reported in the prevention of bacterial meningitis through vaccination programs, challenges still remain with the emergence of antimicrobial resistance, particularly in pneumococci, and the changing epidemiology of the disease. In the past decade, new therapies and strategies for disease management have been examined in experimental animal models. Further clinical experience is warranted to determine the impact these strategies may have in the human population.

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