

Management of Meningitis Caused by Resistant *Streptococcus pneumoniae*

P. Fernández Viladrich

1. INTRODUCTION

Pneumococcal infections are very prevalent worldwide, and *Streptococcus pneumoniae* is a major cause of bacteremia, pneumonia, meningitis, acute otitis media, and acute sinusitis (1). Overall, invasive pneumococcal infections are associated with high morbidity and mortality. Pneumococcal meningitis is a particularly severe form of the disease that accounts for about 10% of invasive pneumococcal infections; its overall annual incidence in industrialized countries is about 1.5 per 100,000 inhabitants (2,3). In children younger than 5 yr, an incidence of 8 per 100,000 was found (3).

Except for epidemics or hyperendemic situations of meningococcal disease, *S. pneumoniae* has long been and continues to be the most frequent cause of community-acquired bacterial meningitis in adults older than 30 yr. In developed countries, the same may be true for children, a population in which *Haemophilus influenzae* type b meningitis has practically disappeared because of the systematic vaccination of infants with the *H. influenzae* conjugated vaccine. Estimates showed that *S. pneumoniae* causes about 50% of community-acquired meningitis, excluding those of the neonatal period (2–4).

Among community-acquired bacterial meningitis, pneumococcal meningitis causes the most morbidity and mortality. In industrialized countries, mortality due to pneumococcal meningitis in adults ranges from 25 to 30%, and these figures have remained constant throughout the antibiotic era in spite of improved critical care medicine. This emphasizes the need to develop new adjunctive therapy (4,5). Serious neurological sequelae are also frequent, especially in children (6,7). To date, the high mortality and morbidity of pneumococcal meningitis has not been caused by failure of antibiotic treatment. However, in view of the current loss of susceptibility of many *S. pneumoniae* strains to β -lactam agents, that situation could become even worse. The prognosis of pneumococcal meningitis, especially in adults, depends more on early diagnosis and early preventive treatment of neurological complications than on antibiotic failure.

2. PATHOGENESIS OF PNEUMOCOCCAL MENINGITIS

Pneumococci reach the central nervous system (CNS) either by a hematogenous route from a distant focus of infection, usually the lower airways with or without pneumonia, or, even more frequently, by direct cerebrospinal fluid (CSF) entrance of bacteria from an infectious focus near the CNS, such as acute otitis media, acute sinusitis, or a cranial fistula. Once organisms have reached the CSF, they quickly multiply, leading to the release of several cytokines. This creates an inflammatory process that increases blood–brain barrier permeability and produces cytotoxic and vasogenic brain edema, intracranial hypertension, ischemia, and neuronal damage. The inflammatory process and consequences may be greatly increased when cell wall fragments are released after bacteriolytic antibiotics are administered. On the other hand, bacterial growth in the meningeal spaces frequently leads to secondary bacteremia, which may contribute to morbidity. Hemodynamic instability or shock, if not properly treated, will worsen the neurological function by lowering the cerebral perfusion pressure and increasing brain ischemia (8–10).

3. CLINICAL MANIFESTATIONS

As in other types of bacterial meningitis, clinical manifestations of pneumococcal meningitis are because of the meningeal inflammation and its neurological consequences, the original source of infection, and possible concurrent primary or secondary septicemia.

Although symptoms and signs of meningismus do not differ from those of other bacterial meningitis, neurological complications are more frequent, especially those related to intracranial hypertension and seizures. Seizures are a complication of bacterial meningitis that have repeatedly been associated with higher mortality and neurological sequelae (4,11–13). In adults, they occur much more frequently in pneumococcal meningitis than in meningitis caused by other pathogens.

About 30% of adults with pneumococcal meningitis convulse (4,14). Moreover, the majority of these seizures occur early in the natural history. In my experience, about 10% of adults with pneumococcal meningitis have already convulsed when first visited, and another 20% convulse after antibiotic treatment has been initiated, usually during the first 24 or 48 h of therapy. Some patients go on to status epilepticus. Additional impairment of consciousness level and signs of brain herniation also often occur after the initiation of antibiotic treatment.

Other neurological complications, such as brain infarcts because of cortical thrombophlebitis or arteritis, occur in about 15% of adults with bacterial meningitis (15). In fact, early death related to the occurrence of one of these complications after CSF has been sterilized by appropriate antibiotic therapy has been a common experience when treating patients with pneumococcal meningitis (and occasionally other types of bacterial meningitis) and may be explained in part by the CSF inflammation described in Section 2. That is why, for more than a decade, to prevent these neurological complications very early adjunctive therapy (*see* Section 5.1.) has been administered to all adult patients with suspected pneumococcal meningitis and to those individuals with bacterial meningitis of any other etiology who show signs of high intracranial hypertension (16).

Of paramount importance when approaching a patient with bacterial meningitis are symptoms and signs caused by a primary focus of infection because they are valuable not only for discovery of the etiologic agent, but also for indication of the most appropriate approach. Thus, when bacterial meningitis is preceded by respiratory symptoms, a classical meningeal pathogen such as meningococcus or pneumococcus is probably the cause (17). Meningitis caused by *Listeria monocytogenes* will not usually be preceded by respiratory symptoms.

Acute bacterial meningitis is the most frequent intracranial complication of acute otitis media at all ages. In adults, this process is almost exclusively caused by *S. pneumoniae*; conversely, about 35% of adult pneumococcal meningitis cases are a complication of an attack of acute otitis media (14,17). On the other hand, a brain abscess is the most frequent intracranial complication of cholesteatomatous chronic otitis media, in which the classical meningeal pathogens are usually not implicated (18).

Thus, in patients with both meningeal signs and otitis, ascertaining the type of otitis has diagnostic and therapeutic implications. A lumbar puncture should be performed without delay if the otitis media is acute, whereas a computed tomographic (CT) brain scan should be performed first if the otitis media is chronic to rule out a suppurative intracranial collection clinically presenting as bacterial meningitis. A pericranial fistula is likely if the patient has suffered, even many years before, cranial or facial trauma, an operation involving either the ethmoid or sphenoid sinuses or the otic cavities, or CSF rhinorrhea or recurrent episodes of bacterial meningitis. *Streptococcus pneumoniae* is also the most frequent cause of bacterial meningitis in this setting, although such other respiratory pathogens as *H. influenzae*, *Neisseria meningitidis*, or streptococci of the *viridans* group may also be the cause (17).

Septicemia may be both the cause and the consequence of the meningeal infection and may cause distant infection, such as arthritis or endocarditis, or shock. Patients with meningitis secondary to pneumococcal septicemia with or without pneumonia or endocarditis have a higher mortality rate (about 50%) than those whose pneumococcal meningitis is secondary to a parameningeal focus. A maculopetechial or purpuric skin rash is characteristic of meningococcal septicemia, although it may also be caused by other microorganisms, including overwhelming pneumococcal infection.

4. DIAGNOSIS

When a diagnosis of community-acquired bacterial meningitis is suspected, a lumbar puncture should be performed immediately, and the CSF opening pressure must be recorded and its aspect observed. For patients with a nonacute clinical course, especially if coma, hemiparesis, or papilledema are found, and in patients who present with a primary focus of infection (e.g., chronic cholesteatomatous otitis media, chronic sinusitis, or dental or anaerobic lung infection) that characteristically complicates with a brain abscess, a CT brain scan should be performed before lumbar puncture (19,20). In these cases, a loading dose of dexamethasone must be immediately administered. Moreover, if acute bacterial meningitis is suspected, empirical antibiotic therapy must be given (after obtaining blood samples for cultures) before performing a CT scan.

As stated in the section on clinical manifestations, seizures are quite frequent in bacterial meningitis, so they do not constitute an indication for brain scanning prior to lumbar puncture if the illness runs an acute course. Because pneumococcal meningitis

usually runs an acute course and rarely coexists with a brain abscess, a cranial CT prior to lumbar puncture is not usually indicated, especially considering that the early administration of dexamethasone is necessary in almost all circumstances (*see* Section 5.1.).

In many cases of community-acquired bacterial meningitis, a pneumococcal etiology can usually be suspected, especially in the adult population, for whom acute otitis media, the presence of a posttraumatic or postsurgical pericranial fistula, or an acute lower respiratory disease (frequently, lobar pneumonia) are the primary infection foci in about 80% of cases. All these entities can easily be diagnosed or strongly suspected based on clinical antecedents and clinical data. In addition, CSF Gram stain is clearly positive in around 80% of patients with pneumococcal meningitis who have not received previous antibiotic therapy. If pneumococcal meningitis is suspected and the Gram stain is negative, a CSF determination of pneumococcal antigen must be performed (21).

5. TREATMENT

Like bacterial meningitis caused by other etiologies, pneumococcal meningitis constitutes a medical emergency that must be rapidly treated to minimize both mortality and neurological sequelae. Cognitive defects have been detected in adults surviving a bout of pneumococcal meningitis without apparent sequelae (6). As mentioned in the introduction, in developed countries the overall mortality from pneumococcal meningitis in adults has remained around 30% (4,14,15,22). This mortality is mainly caused by early neurological complications. When these complications, especially brain herniation, do occur, brain damage is frequently irreversible, and measures aimed at lowering inflammation and cranial hypertension are usually ineffective. Although a general rule for the treatment of bacterial meningitis is not to delay antibiotic treatment because significant delays will certainly increase mortality and neurological sequelae, precocious antibiotic treatment not only may be insufficient to avoid neurological complications, especially those associated with pneumococcal meningitis, but also may favor occurrence of these complications through their bacteriolytic effect. Therefore, because the administration of appropriate adjunctive therapy in these cases may be even more urgent than administration of the antibiotic, I begin with this aspect of therapy.

5.1. Early Adjunctive Therapy

An initial perfusion of mannitol may occasionally be lifesaving by rapidly lowering cranial hypertension (23,24). In deeply comatose patients, consciousness level frequently improves rapidly after mannitol administration. This improvement may be manifested by progression from coma to an agitated state. Moreover, improvement of bradycardia and the respiratory rhythm irregularities that these patients sometimes present may also be observed. Although the routine use of mannitol in acute bacterial meningitis is not usually recommended, I think that there might be some rationale for using it in every case of suspected pneumococcal meningitis.

As reported, the practice of cranial CT does not discriminate which patients will have cerebral herniation after a lumbar puncture, so some patients with a normal cranial CT will suffer this life-threatening complication (25). On the other hand, routine cranial CT in suspected meningitis may significantly delay antibiotic therapy, thereby

increasing the probability of neurological or cognitive sequelae (19). For more than a decade, it has been my usual practice to administer adjunctive therapy with mannitol (a bolus of 0.5–1 g per kilogram body weight) and dexamethasone (a loading dose of 8–16 mg followed by doses of 4 mg every 6 h for 48 h) immediately after lumbar puncture of adults with bacterial meningitis who show clinical signs of severe intracranial hypertension or a CSF opening pressure higher than 30 cm water, as well as to all suspected cases of pneumococcal meningitis regardless of CSF opening pressure. Such treatment has been administered to many patients with bacterial meningitis without significant adverse events.

With regard to anti-inflammatory treatment, there is general agreement as to the convenience of administering dexamethasone to children with bacterial meningitis (26). Dexamethasone has been shown to reduce neurological and audiologic sequelae in children with meningitis caused by *H. influenzae* type b (27). The same may be true for pneumococcal meningitis in children provided the dexamethasone is given before or at the same time as antibiotic therapy. The administration of dexamethasone during the first 48 h of therapy has not been associated with significant adverse events in this population (28). On the other hand, early dexamethasone therapy has been proved to reduce mortality of adult patients with pneumococcal meningitis to 14% (29). A study published by Girgis et al. in 1989 showed that early dexamethasone therapy reduced mortality, but because of several deficiencies, it was not seriously considered (30). Since 1987, I have been treating pneumococcal meningitis in adults with the early administration of mannitol and dexamethasone and with intravenous sodium phenytoin to prevent seizures (a loading dose of 18 mg per kilogram body weight followed by standard doses every 8 h), with an attributable mortality of 12% (16).

Regarding the administration of dexamethasone in bacterial meningitis, and especially in pneumococcal meningitis, there are several considerations. First, early administration of corticosteroids constitutes an excellent symptomatic therapy, contributing to accelerate improvement of such cranial hypertension symptoms as headache, which is frequently very intense and difficult to control with analgesic treatment, as well as improvement of consciousness level. Fever is also more quickly abated by using these drugs. These beneficial effects of corticosteroids have never been considered as end points in comparative studies, but I think they are worthy of consideration in view of the intense suffering of patients in the initial phases of meningeal inflammation. Second, side effects of corticosteroids, especially clinically significant gastrointestinal hemorrhage, are infrequent, especially if the corticosteroids are administered for only 48 h (28,29). Third, corticosteroids impair the passage of several antibiotics, such as β -lactam agents and vancomycin, through the blood–brain barrier. This effect may have negative consequences in cases of bacterial meningitis in which there is a low therapeutic index because of the class of antibiotic used (e.g., vancomycin) or to the susceptibility of the causal organism (e.g., moderate resistance to β -lactam agents). However, this problem will probably be minimized if dexamethasone use is limited to the first 48 h of treatment, when the permeability of the blood–brain barrier is expected to be clearly increased by the inflammatory process. Although a dosage of 10 mg every 6 h for 4 d has recently been recommended for bacterial meningitis in adults (29), based on experience, I believe that both lower dosage and shorter treatment are probably sufficient for this population.

If adjunctive therapy is appropriately conducted, many patients with severe neurological disease will improve rapidly, and the need for more aggressive measures may be avoided. However, hospitalization in an intensive care unit is mandatory for those patients who convulse in spite of adjunctive therapy; for those with other severe neurological complications that require mechanical support, hyperventilation, and monitoring of cranial hypertension; and, obviously, for those patients who have hemodynamic instability or shock (31).

5.2. Antibiotic Treatment

5.2.1. Historical Perspective

It is well known that, over the past 30 years or more, pneumococci have developed resistance to several antimicrobial agents, including penicillin, cephalosporins, chloramphenicol, trimethoprim-sulfamethoxazole, erythromycin, and other drugs. But, in terms of therapy and especially for the treatment of meningitis, the most important problem has been the development of resistance to penicillin. This is because penicillin was the time-honored treatment for decades for pneumococcal infections, and alternative drugs were only necessary in penicillin-allergic patients.

An interesting fact is that, shortly after the introduction of penicillin in 1940, the first strain with decreased susceptibility to penicillin was produced in the laboratory (32). However, the first clinical isolate did not appear until more than 20 yr later in Boston (33). In the late 1960s, pneumococcal strains with moderate penicillin resistance (defined as those pneumococci with minimum inhibitory concentrations [MICs] of penicillin G of 0.1 to 1 $\mu\text{g/mL}$) were isolated in Australia and New Guinea (34–36). Some cases of meningitis caused by pneumococci with those levels of resistance responded to high dosages of penicillin, but others failed to respond (37). This happened because attainable peak CSF levels of penicillin—around 1 $\mu\text{g/mL}$ (38)—are close to the MICs of those partially penicillin-resistant pneumococci. So, penicillin G had to be discarded for empirical treatment of suspected pneumococcal meningitis.

In the 1970s, an epidemic of high-level penicillin-resistant pneumococci (with MICs of penicillin G $> 1 \mu\text{g/mL}$) that were also resistant to chloramphenicol and other antibiotics was reported in pediatric wards in South Africa (39,40). The patients with meningitis caused by those strains who received penicillin or chloramphenicol died. At present, most penicillin-resistant pneumococci are also resistant to chloramphenicol, and even when they show susceptibility to this antibiotic by usual methods of susceptibility, they are tolerant, and the clinical response to treatment with this antibiotic has been poor (41). So, chloramphenicol, once the elective alternative for pneumococcal meningitis in patients allergic to penicillin, must not be used as either empirical treatment of suspected pneumococcal meningitis or treatment of cases caused by pneumococci with any degree of penicillin resistance.

The solution to this problem seemed to be the third-generation cephalosporins—cefotaxime and ceftriaxone, which remained active against moderately penicillin-resistant pneumococci. However, penicillin-resistant pneumococci show diminished sensitivity to all β -lactam agents, including cefotaxime and ceftriaxone (42), and failures with the standard doses of these antibiotics soon occurred when the illnesses were caused by pneumococcal strains with MICs of cefotaxime greater than or even equal to 0.5 $\mu\text{g/mL}$ (37,43–57).

At present, pneumococci with MICs of cefotaxime of 1 µg/mL are defined as partially cefotaxime resistant, and those with MICs greater than 1 µg/mL are defined as highly cefotaxime resistant (58). However, a pneumococcus showing an MIC of cefotaxime of 0.5 µg/mL might have a minimal bactericidal concentration of 1 or even 2 µg/mL. Therefore, I consider that, for therapeutic purposes, it should be classified as cefotaxime nonsusceptible. After one of my patients with penicillin-resistant pneumococcal meningitis showed a rapid response to high-dose cefotaxime therapy (37), such treatment was considered suitable for penicillin-resistant and partially cefotaxime-resistant pneumococcal meningitis in adults (37,59).

Other authors also obtained good results in such cases with even lower doses of cefotaxime (60). However, high-dose cefotaxime therapy has not reached initial general acceptance, probably because there is concern about the administration of higher-than-conventional doses and, especially, because a few cases of meningitis caused by pneumococci with a high level of cefotaxime resistance (MICs of cefotaxime from 4 to 32 µg/mL) occurred in the United States (47–49).

Initially, the solution to the problem of resistance to β-lactam agents seemed to be the use of vancomycin, an antibiotic to which all pneumococci remained (and still remain) susceptible, with MICs ranging between 0.25 and 1 µg/mL. However, surprisingly for the medical community, several clinical failures were documented when vancomycin was used in conjunction with dexamethasone (61). Those failures were mainly because of insufficient antibiotic penetration into CSF, due both to individual variability in its passing through the blood–brain barrier and to the effect of dexamethasone, which was shown to reduce CSF vancomycin penetration (62,63). Since this experience, the recommendation is that vancomycin not be used alone for treatment of pneumococcal meningitis; based on a few studies performed both in vitro and in the rabbit model of meningitis, combined antibiotic regimens have been recommended for both empirical treatment and treatment of those cases caused by β-lactam-resistant pneumococcal strains (64–67).

5.2.2. Initial Empirical Therapy

Initial empirical therapy refers to the initial treatment for a patient with either suspected or diagnosed pneumococcal meningitis (e.g., compatible clinical features plus one of the following: CSF Gram stain showing typical Gram-positive diplococci, CSF-positive pneumococcal antigen, or CSF culture yielding pneumococci with unknown antibiotic susceptibility). Empirical therapy must also be given to patients with suspected pneumococcal meningitis based on clinical grounds only in cases when urgent CSF Gram stain could not be performed or there is a contraindication for performing an immediate lumbar puncture.

Although antibiotic treatment must be immediately instituted in those patients with skin lesions suggestive of meningococcal sepsis, in cases of pneumococcal meningitis, it can probably be delayed for some minutes to perform a CSF Gram stain and to institute preantibiotic adjunctive therapy. I review some possibilities for the empirical antibiotic therapy.

5.2.2.1. HIGH-DOSE CEFOTAXIME THERAPY

If the patient is not allergic to β-lactam agents, the empirical therapy for pneumococcal meningitis should always include a third-generation cephalosporin such as

cefotaxime or ceftriaxone. As mentioned in the historical perspective, neither penicillin nor chloramphenicol must be administered for empirical therapy. These cephalosporins will also cover the other respiratory pathogens usually causing community-acquired bacterial meningitis. Treatment with either standard intravenous dose of cefotaxime (150–200 mg/kg body weight per day with a maximum of 12 g) or ceftriaxone (100 mg/kg body weight per day with a maximum of 4 g; higher doses of ceftriaxone are not recommended because of potential side effects, especially biliary precipitation stones) has sometimes failed to cure some cases of meningitis caused by pneumococci partially resistant to cefotaxime (MICs = 1 µg/mL) and even with some diminution of sensitivity (MIC = 0.5 µg/mL) (37,56,57). For almost two decades, I have used high doses of cefotaxime (300–350 mg/kg body weight per day to a maximum of 24 g) as sole therapy for the empirical treatment of pneumococcal meningitis in adults, and this therapy was safe and effective for cefotaxime-resistant cases (MICs of cefotaxime up to 2 µg/mL), with all experiencing a good response with sterile CSF cultures.

In Spain, the percentage of pneumococcal strains that were resistant to cefotaxime was 21% in 2000 (68). Of these, 17% were partially resistant (MICs of cefotaxime of 1 µg/mL), and 6% were highly resistant (MICs of cefotaxime equal to or higher than 2 µg/mL). The majority of these resistant strains showed MICs of cefotaxime of 2 µg/mL. Pneumococci with MICs of cefotaxime higher than 2 µg/mL have been not found in adults, and in more than 20 years in the era of pneumococcal resistance, not one case of meningitis caused by such a strain has been found in Spain. However, in 2000, a few pneumococcal strains with MICs of cefotaxime equal to or even higher than 4 µg/mL were isolated from invasive pneumococcal disease in children younger than 5 yr (68,69).

At present, these limits in levels of cefotaxime resistance are probably found in the majority of areas in the world. It is very improbable that cases with the aforementioned levels of cefotaxime resistance cannot be controlled with such high doses of cefotaxime during the first 24 to 48 h of treatment, when the blood–brain barrier must remain quite permeable, and the results of susceptibility tests can be obtained.

In spite of the above considerations, high-dose cefotaxime therapy might occasionally fail when CSF levels do not sufficiently exceed the MIC of the causal strain (70) because of individual variability of CSF levels or when there is an MIC of cefotaxime equal to or greater than 4 µg/mL. Therefore, although this is my present approach for empirical treatment in the adult population in my area, use a combination of cefotaxime and vancomycin (*see* Section 5.2.2.2.) for empirical treatment while awaiting the results of cultures and susceptibility tests. However, combined empirical therapy must only be given in those cases that I defined in this section as either practically certain or really probable pneumococcal meningitis.

5.2.2.2. THIRD-GENERATION CEPHALOSPORIN PLUS VANCOMYCIN

The combination of standard doses of cefotaxime or ceftriaxone plus vancomycin for empirical therapy of pneumococcal meningitis was recommended for the first time in 1994 (64). This antibiotic combination was synergistic in studies *in vitro* (71), in the rabbit model of meningitis (72), and in an *in vitro* study using CSF of children treated with this antibiotic combination (73). However, these experiences have been limited.

In another in vitro study, the combination of cefotaxime plus vancomycin was found to be indifferent against 26 pneumococcal strains (74); in work with colleagues, I found this combination to be bactericidal, but not synergic (75). In any case, this antibiotic combination has been increasingly used over the last years, and it constitutes the current standard recommendation for empirical treatment of suspected pneumococcal meningitis, especially in children (67). However, I believe it is important to keep in mind some considerations regarding this antibiotic combination:

1. Little clinical experience with this therapy has been published (76,77).
2. It does not seem to be synergistic against all strains of pneumococci.
3. It is possible that neither of the two antibiotics reach the necessary CSF levels for rapid bactericidal activity. Vancomycin at the recommended dosage for adult patients (30 mg/kg body weight per day) does not reach reliable CSF levels, especially if dexamethasone is administered concurrently (61), and CSF cefotaxime levels might also be insufficient for some cephalosporin-resistant pneumococcal strains (70). That is why I recommend that high-dose cefotaxime (e.g., around 350 mg/kg body weight per day, with a maximum dose of 24 g per day) always be administered initially to adults with suspected pneumococcal meningitis.
4. In contrast, standard doses of cefotaxime or ceftriaxone are sufficient for empirical treatment in children because the standard dosage of vancomycin they are receiving for treatment of meningitis (60 mg/kg body weight per day, double that of adults) is sufficient to cure the infection even if dexamethasone is given concurrently (73).

5.2.2.3. THIRD-GENERATION CEPHALOSPORIN PLUS RIFAMPIN

The combination of cefotaxime or ceftriaxone with rifampin has been recommended in lieu of therapy with cephalosporin plus vancomycin for empirical treatment of pneumococcal meningitis when dexamethasone was given concurrently (64–66), especially because CSF penetration of rifampin, unlike that of vancomycin, is unaffected by dexamethasone administration (62). At present, when it is known that adjunctive dexamethasone therapy is obligatory (29), this therapeutic recommendation could even be reinforced. Rifampin is bactericidal against *S. pneumoniae*, and around 99% of pneumococci remain susceptible, with MICs equal to or less than 0.12 µg/mL (69,78–80). CSF levels of rifampin, when administered at maximum dosage (about 900 mg/d for adults, 20 mg/kg body weight per day for children), are around 1 µg/mL (73,81), which is sufficient for reaching appropriate activity against *S. pneumoniae*.

On the other hand, rifampin reduced early mortality when compared with ceftriaxone in experimental pneumococcal meningitis in mice by reducing the release of inflammatory cytokines (82). In another experiment in rabbits, it reduced the release of reactive oxygen species in CSF (83). However, rifampin cannot be used as monotherapy because of rapid development of resistance, and it must be administered in combination with another antibiotic.

Nevertheless, in vitro studies with the combination of rifampin with β-lactams or vancomycin have led to conflicting results. In an in vitro study using antibiotic combinations at clinically achievable concentrations in CSF, rifampin frequently reduced the killing activity of ceftriaxone, vancomycin, and imipenem against 15 penicillin-resistant pneumococcal strains with MICs of ceftriaxone of 0.5–1 µg/mL (74). In a study with colleagues, we found the combination ceftriaxone-rifampin antagonistic in vitro (75). However, in another study using much lower concentrations of rifampin, Barakett

et al. reported that rifampin combined with vancomycin or cefotaxime usually had synergistic or indifferent activity (84); in another study, CSF concentrations above those observed in humans with usual dosage regimens led to a decrease in bacterial killing (85).

In a report of vancomycin-rifampin therapy in the animal model of meningitis, rifampin activity was reduced during the first few hours of therapy, showed moderately bactericidal activity compared with that of ceftriaxone or vancomycin, and killing rates comparable to those of β -lactam antibiotics could not be obtained by increasing the dose of rifampin (72). In contrast, in an in vitro study using CSF of children treated with various antibiotic combinations, the combination of ceftriaxone plus rifampin was synergistic, with treatment with rifampin significantly increasing the bactericidal activity of ceftriaxone against two cefotaxime-resistant strains of *S. pneumoniae* (either partially ceftriaxone resistant or highly ceftriaxone resistant) (73).

To my knowledge, clinical experience with the combination of cephalosporins with rifampin for empirical therapy of suspected pneumococcal meningitis is lacking. At present, it is generally not recommended for empirical therapy because clinical experience is lacking, concerns exist as to whether it might reduce the bactericidal activity of β -lactam agents, and the possibility of selection for rifampin resistance exists. However, if chosen for empirical treatment in combination with a third-generation cephalosporin, I also would advise that a high dose of cefotaxime be administered because if insufficient levels of cephalosporin were reached in CSF, it could constitute real monotherapy with rifampin, possibly leading to the rapid development of rifampin resistance during treatment.

In spite of the above-mentioned negative considerations, I believe that, if a rifampin-susceptible pneumococcus is the cause and high-dose cefotaxime therapy was used, this antibiotic combination may be effective for cefotaxime-resistant pneumococcal meningitis, provided the MICs of cefotaxime were no higher than 4 $\mu\text{g/mL}$.

5.2.2.4. VANCOMYCIN PLUS RIFAMPIN

For patients allergic to β -lactams, I favor the combination of vancomycin and rifampin for empirical therapy. In the rabbit model of experimental meningitis, my group found that this combination was bactericidal—although not synergic—and effective against cefotaxime-resistant pneumococci, and that CSF vancomycin levels were not reduced by dexamethasone (86). Moreover, it cured some children who had experienced therapeutic failure when treated with other antibiotics (49,52,55,87); my group has administered this antibiotic combination with good results to several adults with pneumococcal meningitis (88). However, because failures can occur in the case of low CSF vancomycin levels, strict monitoring of both CSF microbiological parameters and serum vancomycin levels is necessary. My impression is that the regimen of vancomycin plus rifampicin is somewhat better than that of vancomycin alone, especially concomitant with dexamethasone therapy. CSF bactericidal titers achieved with this combination appear moderately higher than those achieved with vancomycin alone (61,88).

5.2.3. Therapy for Pneumococcal Meningitis if Susceptibility Is Known

Appropriate antibiotic treatment of pneumococcal meningitis requires knowledge of the causal strain's susceptibility to penicillin and to broad-spectrum cephalosporins. If a pneumococcus is growing on CSF culture, it is possible to obtain preliminary infor-

mation about its susceptibility to β -lactam agents in less than 24 h by performing an Etest® (AB Biodisk, Solna, Sweden) directly on seeded culture plates. After results of susceptibility tests are known, empirical antibiotic therapy can be modified.

If vancomycin or rifampin is given in conjunction with a third-generation cephalosporin, they must be discontinued if the causal strain is sensitive to penicillin or third-generation cephalosporins. They must also be discontinued if CSF and blood cultures are sterile at 48–72 h of incubation whether or not the patient has received prior antibiotic therapy. If the patient received prior treatment with a β -lactam antibiotic (penicillin or cephalosporin), it can be assumed that, if a bacterial agent is the cause, it will be sensitive to β -lactams; if not, it is very improbable that the patient has pneumococcal meningitis.

5.2.3.1. PENICILLIN-SENSITIVE PNEUMOCOCCAL MENINGITIS

Penicillin remains the therapy of choice for susceptible strains of pneumococci, and alternative drugs are only necessary in penicillin-allergic patients. Penicillin should be given at doses of 300,000 U/kg body weight (2 to 4 MU in adults) scheduled every 4 h intravenously. As an alternative, treatment with a standard dose of ceftriaxone may occasionally be convenient for the patient's comfort (especially to avoid catheter phlebitis); this dose may be given once a day intramuscularly if necessary. This is my usual practice for adult patients, and this therapy has proved safe and effective.

Chloramphenicol constitutes the therapy of choice for penicillin-allergic patients with penicillin-susceptible pneumococcal meningitis because the majority (if not all) of penicillin-sensitive pneumococci are also chloramphenicol sensitive, and chloramphenicol must replace empirical vancomycin therapy. As mentioned in the historical perspective section, chloramphenicol must not be given in penicillin-resistant cases even if the causal strain appeared susceptible by the Kirby-Bauer method (41). In this case, determinations of minimal bactericidal concentrations of this antibiotic should be performed before it is selected as an alternative therapy.

5.2.3.2. PENICILLIN-RESISTANT AND CEFOTAXIME-SENSITIVE PNEUMOCOCCAL MENINGITIS

As mentioned in Section 5.2.1., patients infected with strains with decreased susceptibility to penicillin (MICs of penicillin equal to or higher than 0.12 $\mu\text{g/mL}$) should not be treated with this antibiotic. In such cases, standard-dose cefotaxime or ceftriaxone is the therapy of choice for those with MICs of cefotaxime equal to or less than 0.25 $\mu\text{g/mL}$. Cases with MIC of cefotaxime of 0.5 $\mu\text{g/mL}$, although defined as sensitive, have a significant loss of susceptibility, and I recommend they be treated with high-dose cefotaxime (*see* Section 5.2.1.).

5.2.3.3. PENICILLIN-RESISTANT AND CEFOTAXIME-RESISTANT PNEUMOCOCCAL MENINGITIS

If the causal strain shows any degree of penicillin and cephalosporin resistance, the empirical treatment that was initially administered must be continued until completion of treatment if the patient does well. However, a control lumbar puncture should always be performed at 24–48 h after the start of antibiotic therapy to document the sterility of CSF culture and to test CSF antibiotic levels or bactericidal titers if possible. A repeated lumbar puncture is also recommended if signs of clinical recrudescence occur at any time during the treatment.

In cefotaxime-resistant pneumococcal meningitis in adults, it has been my usual practice to continue with the high doses of cefotaxime initially administered if clinical evolution is good and to add vancomycin if there is some doubt about a satisfactory

response. High-dose cefotaxime therapy has been effective in curing several of my patients with meningitis caused by pneumococci with MICs to cefotaxime of 1 and 2 $\mu\text{g/mL}$ (37). However, in one recent case with MICs of cefotaxime of 2 $\mu\text{g/mL}$, vancomycin was added on d 5 in response to persistent fever, meningeal signs, and inflammatory CSF parameters despite negative CSF Gram stain and culture. That patient experienced an immediate response to the addition of vancomycin.

If the combination of cephalosporin plus vancomycin was initially given to an adult patient, it is mandatory to determine serum vancomycin levels at 36–48 h of therapy to ensure trough serum vancomycin levels of about 10 $\mu\text{g/mL}$ and to modify the dosage if necessary. This is important because there is quite individual variability in vancomycin pharmacokinetics, so occasionally a patient receiving the appropriate standard vancomycin dosage (15 mg/kg body weight every 12 h) could possibly have either insufficient or excessive serum levels. Determination of vancomycin levels is less important in the pediatric population.

In case of suspected therapeutic failure (e.g., reappearance of fever and recrudescence of meningeal signs or, especially, if positive CSF culture persists at 24–48 h of treatment), one of the following alternative therapies may be considered.

5.3. Alternative Therapies for Penicillin- and Cefotaxime-Resistant Pneumococcal Meningitis

For therapeutic failure in a case of penicillin- and cefotaxime-resistant pneumococcal meningitis, some possible alternatives are as follows: If the patient is not receiving vancomycin, add this antibiotic to the regimen initially administered. If the patient is already receiving an appropriate dosage of vancomycin (appropriate serum levels documented), any of the following therapeutic regimens could be effective:

1. Change to high-dose cefotaxime therapy if the patient was receiving a standard dosage of cefotaxime or ceftriaxone.
2. Add rifampin to the regimen of high-dose cefotaxime plus vancomycin.
3. Add intrathecal vancomycin (10–20 mg every 24 or 48 h) to the systemic regimen (49,53,55,89).
4. Change to imipenem with or without rifampin. Imipenem MICs tend to be lower than those of cefotaxime against penicillin-resistant pneumococci, but because the dosage of imipenem is lower (maximum 4 g/24 h), it does not seem to me that it would be able to significantly ameliorate the CSF activity obtained with high-dose cefotaxime. However, some children with cefotaxime-resistant pneumococcal meningitis have been cured with imipenem alone (43) or combined with rifampin (54). On the other hand, the potential risk of seizures should be taken into account when treating bacterial meningitis with imipenem (50).
5. Meropenem could be considered. Dosage of meropenem is somewhat higher (maximum 6–8 g/24 h) than that of imipenem, and CSF levels of around 3 $\mu\text{g/mL}$ can be reached (90). However, meropenem MICs tend to be two- to fourfold higher than those of imipenem (91), so I do not believe it is a good alternative for cefotaxime-resistant pneumococcal meningitis. The same might be said about fourth-generation cephalosporins such as cefpirome or cefepime.
6. Some of the new quinolones could perhaps be tested for a desperate case. Some of the newer quinolones have been very effective in the animal model of β -lactam-resistant pneumococcal meningitis (92–97), and trovafloxacin was found safe and similar to ceftriaxone with or without vancomycin in a series of bacterial meningitis in children (98). However, great concern exists about its tendency to develop antibiotic resistance (99). Resistance to

levofloxacin has developed during treatment for pneumococcal pneumonia (100,101); information on a case of fatal meningitis caused by levofloxacin-resistant *S. pneumoniae* has been published (102); and at present, almost 1.5% of *S. pneumoniae* strains from Spain are resistant to this antibiotic (68,103).

7. Some new antibiotics, such as linezolid (104), against Gram-positive bacteria could perhaps be useful for β -lactam-resistant pneumococcal meningitis in the future.

5.4. Duration of Treatment

The recommended length of therapy for pneumococcal meningitis is 10 to 14 d of effective antibiotic therapy. If the patient does well, I treat this illness for 10 d regardless of the susceptibility characteristics of the causal strain. My group and others have demonstrated that β -lactam-resistant pneumococcal meningitis is not more severe than penicillin-susceptible pneumococcal meningitis (37,105).

6. PREVENTION

Bacterial meningitis will continue to be a serious disease. The best efforts must be directed toward prevention. Thus, pneumococcal vaccines must be given. The routine administration of heptavalent conjugate pneumococcal vaccine to infants will probably lower the incidence of pneumococcal meningitis in this population (106–108). Moreover, the 23-serotype polysaccharide pneumococcal vaccine must be administered to all adult patients who have the known indications. If the patient has a CSF pericranial fistula, he or she must promptly receive surgery to avoid new episodes of bacterial meningitis. In such a circumstance, pneumococcal vaccination has been inefficient in preventing recurrent episodes of pneumococcal meningitis, even when caused by pneumococcal strains of the serotypes included in the vaccine (109).

REFERENCES

1. Musher DM. *Streptococcus pneumoniae*. In: Mandell GM, Bennet JE, Dolin R (eds.). Principles and Practice of Infectious Diseases. 4th ed. New York: Churchill Livingstone, 1995, pp. 1811–1826.
2. Schuchat A, Robinson K, Wenger JD, et al. Bacterial meningitis in the United States in 1995. N Engl J Med 1997; 337:970–976.
3. Spanjaard L, van der Ende A, Rumke H, Dankert J, van Alphen L. Epidemiology of meningitis and bacteraemia due to *Streptococcus pneumoniae* in The Netherlands. Acta Pediatr Suppl 2000; 89:22–26.
4. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J Med 1993; 328:21–28.
5. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. Ann Intern Med 1998; 129:862–869.
6. van de Beek D, Schmand B, de Gans J, et al. Cognitive impairment in adults with good recovery after bacterial meningitis. J Infect Dis 2002; 186:1047–1052.
7. Kornelisse RF, Westerbeek CML, Spoor AB, et al. Pneumococcal meningitis in children: prognostic indicators and outcome. Clin Infect Dis 1995; 21:1390–1397.
8. Saez-Llorens X, Ramilo O, Mustafa MM, Mertsola J, McCracken GH Jr. Molecular pathophysiology of bacterial meningitis: current concepts and therapeutic implications. J Pediatr 1990; 116:671.
9. Quagliarello V, Scheld WM. Bacterial meningitis: pathogenesis, pathophysiology, and progress. N Engl J Med 1992; 327:864–872.

10. Pfister HW, Fontana A, Täuber MG, Tomasz A, Sheld WM. Mechanisms of brain injury in bacterial meningitis: workshop summary. *Clin Infect Dis* 1994; 19:463–479.
11. Viladrich PF. Enfermedad Meningocócica en Adolescentes y Adultos (Hospital de Bellvitge, 1977–1990) [doctoral thesis]. Universidad de Barcelona, Spain, 1993.
12. Lacroix J, Deal C, Gauthier M, Rousseau E, Farrell FA. Admissions to a pediatric intensive care unit for status epilepticus: a 10-year experience. *Crit Care Med* 1994; 22: 827–832.
13. Casado Flores J, García Teresa MA, Cambra F, et al. Estudio prospectivo multicéntrico de la meningitis bacteriana grave pediátrica. *An Esp Pediatr* 1997; 47:466–472.
14. Viladrich PF, Buenaventura I, Gudíol F, et al. Meningitis neumocócica del adulto. Estudio de 141 episodios. *Med Clin (Barc)* 1986; 87:569–574.
15. Pfister HW, Feiden W, Einhüpl KM. Spectrum of complications during bacterial meningitis in adults. *Arch Neurol* 1993; 50:575–581.
16. Viladrich PF, Gudíol F. Avances en las infecciones del sistema nervioso central producidas por bacterias grampositivas. *Rev Clin Esp* 1994; 194:847–852.
17. Viladrich PF, Gudíol F, Rufí G, et al. Meningitis bacteriana. Etiología y focos de origen de 482 episodios. *Med Clin (Barc)* 1986; 86:615–620.
18. Ariza J, Casanova A, Viladrich PF, et al. Etiological agent and primary source of infection in 42 cases of focal intracranial suppuration. *J Clin Microbiol* 1986; 24:899–902.
19. Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med* 2001; 345:1727–1733.
20. van Crevel H, Hijdra A, de Gans J. Lumbar puncture and the risk of herniation: when should we first perform CT? *J Neurol* 2002; 249:129–137.
21. Marcos MA, Martínez E, Almela M, Mensa J, Jiménez de Anta MT. New rapid antigen test for diagnosis of pneumococcal meningitis. *Lancet* 2001; 357:1499–1500.
22. Milhaud D, Bernardin G, Rastello M, Mattei M, Blard JM. Meningites bacteriennes de l'adulte en réanimation médicale. Analyse clinique et étude des facteurs pronostiques. *Presse Med* 1996; 25:353–359.
23. Horwitz SJ, Boxerbaum B, O'Bell J. Cerebral herniation in bacterial meningitis in childhood. *Ann Neurol* 1980; 7:524–528.
24. McDonald JT, Uden DL. Intravenous glycerol and mannitol therapy in children with intracranial hypertension. *Neurology* 1982; 32:437–440.
25. Kastenbauer S, Winkler F, Pfister HW. Cranial CT before lumbar puncture in suspected meningitis. *N Engl J Med* 2002; 346:1248–1251.
26. Coyle PK. Glucocorticoids in central nervous system bacterial infection. *Arch Neurol* 1999; 56:796–801.
27. Odio CM, Faingezicht I, Paris M, et al. The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. *N Engl J Med* 1991; 324:1525–1531.
28. McIntyre PB, Berkey CS, King SM, et al. Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988. *JAMA* 1997; 278:925–931.
29. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002; 347:1549–1556.
30. Girgis NI, Farid Z, Mikhail IA, et al. Dexamethasone treatment for bacterial meningitis in children and adults. *Pediatr Infect Dis J* 1989; 8:848–851.
31. Alvarez Lerma F, Cisneros JM, Viladrich PF, et al. Indications for admission to the intensive care service of adult patients with severe infections. *Enferm Infecc Microbiol Clin* 1998; 16:423–430.
32. Eriksen KR. Studies on induced resistance to penicillin in a pneumococcus type 1. *Acta Pathol Microbiol Scand* 1945; 22:398–405.

33. Kislac JV, Razavi LMB, Daly AK, Finland M. Susceptibility of pneumococci to nine antibiotics. *Am J Med Sci* 1965; 250:262–268.
34. Hansman D, Bullen MM. A resistant pneumococcus. *Lancet* 1967; 2:264–265.
35. Hansman D, Glasgow H, Surt J, Devitt HL, Douglas R. Increased resistance to penicillin of pneumococci isolated from man. *N Engl J Med* 1971; 284:175–177.
36. Hansman D, Devitt HL, Miles H, Riley I. Pneumococci relatively resistant to penicillin in Australia and New Guinea. *Med J Aust* 1974; 2:353–356.
37. Viladrich PF, Gudiol F, Liñares J, Rufí G, Ariza J, Pallarés R. Characteristics and antibiotic therapy of adult meningitis due to penicillin-resistant pneumococci. *Am J Med* 1988; 84:839–846.
38. Hieber JP, Nelson JD. A pharmacologic evaluation of penicillin in children with purulent meningitis. *N Engl J Med* 1977; 297:410–413.
39. Appelbaum PC, Scragg JN, Bowen AJ, Bhamjee A, Hallet AF, Cooper RC. *Streptococcus pneumoniae* resistant to penicillin and chloramphenicol. *Lancet* 1977; 2:995–997.
40. Jacobs MR, Koornhof HJ, Robins-Browne RM, et al. Emergence of multiply resistant pneumococci. *N Engl J Med* 1978; 299:735–740.
41. Frieland IR, Klugman KP. Failure of chloramphenicol therapy in penicillin-resistant pneumococcal meningitis. *Lancet* 1992; 339:405–408.
42. Liñares J, Alonso T, Perez JL, et al. Decreased susceptibility of penicillin-resistant pneumococci to 24 β -lactam antibiotics. *J Antimicrob Chemother* 1992; 30:279–288.
43. Asensi F, Pérez-Tamarit D, Otero MC, et al. Imipenem-cilastatin therapy in a child with meningitis caused by a multiply resistant pneumococcus. *Pediatr Infect Dis J* 1989; 8:895.
44. Alonso J, Madrigal V, García-Fuentes M. Recurrent meningitis from a multiply resistant *Streptococcus pneumoniae* strain treated with erythromycin. *Pediatr Infect Dis J* 1991; 10:256.
45. Bradley JS, Connor JD. Ceftriaxone failure in meningitis caused by *Streptococcus pneumoniae* with reduced susceptibility to β -lactam antibiotics. *Pediatr Infect Dis J* 1991; 10:871–873.
46. Gellert G, Bock BV, Meyers H, Robertson C, Ehling LR. Penicillin-resistant pneumococcal meningitis in an HIV-infected man. *N Engl J Med* 1991; 325:1047–1048.
47. Sloas MM, Barrett FF, Chesney PJ, et al. Cephalosporin treatment failure in penicillin- and cephalosporin-resistant *Streptococcus pneumoniae* meningitis. *Pediatr Infect Dis J* 1991; 1:662–666.
48. Friedland IR, Shelton S, Paris M, et al. Dilemmas in diagnosis and management of cephalosporin-resistant *Streptococcus pneumoniae* meningitis. *Pediatr Infect Dis J* 1993; 12:196–200.
49. Leggiadro RJ, Barret FF, Chesney PJ, Davis Y, Tenover FC. Invasive pneumococci with high level penicillin and cephalosporin resistance at a Mid-South Childrens Hospital. *Pediatr Infect Dis J* 1994; 13:320–322.
50. Asensi F, Otero MC, Pérez-Tamarit D, et al. Risk/benefit in the treatment of children with imipenem-cilastatin for meningitis caused by penicillin-resistant pneumococcus. *J Chemother* 1993; 5:133–134.
51. Kleiman MB, Weinberg GA, Reynolds JK, Allen SD. Meningitis with β -lactam-resistant *Streptococcus pneumoniae*: the need for early repeat lumbar puncture. *Pediatr Infect Dis J* 1993; 12:782–784.
52. John CC. Treatment failure with use of a third-generation cephalosporin for penicillin-resistant pneumococcal meningitis: case report and review. *Clin Infect Dis* 1994; 18:188–193.
53. Catalán MJ, Fernández JM, Vázquez A, Varela de Seijas E, Suárez A, Bernaldos de Quirós JCL. Failure of cefotaxime in the treatment of meningitis due to relatively resistant *Streptococcus pneumoniae*. *Clin Infect Dis* 1994; 18:766–769.

54. Guibert M, Chahime H, Petit J, Odievre M, Labrune P. Failure of cefotaxime treatment in two children with meningitis caused by highly penicillin-resistant *Streptococcus pneumoniae*. *Acta Paediatr* 1995; 84:831–833.
55. Lonks JR, Durkin MR, Meyerhoff AN, Medeiros AA. Meningitis due to ceftriaxone-resistant *Streptococcus pneumoniae*. *N Engl J Med* 1995; 332:893–894.
56. Flórez C, Silva G, Martín E. Cefotaxime failure in pneumococcal meningitis caused by a susceptible isolate. *Pediatr Infect Dis J* 1996; 15:723.
57. Michaus ML, Pérez-Díaz L, de Pablos M, Lezaun MJ, López-Bayón J. Fallo terapéutico con cefotaxima en dosis altas en meningitis neumocócica. *Enferm Infecc Microbiol Clín* 1997; 15:276–277.
58. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing; Ninth Informational Supplement. Wayne, PA: National Committee for Clinical Laboratory Standards, 1999. M100-S9.
59. Viladrich PF, Cabellos C, Pallarés R, et al. High doses of cefotaxime in treatment of adult meningitis due to *Streptococcus pneumoniae* with decreased susceptibilities to broad-spectrum cephalosporins. *Antimicrob Agents Chemother* 1996; 40:218–220.
60. Tan TQ, Schutze GE, Mason EO, Kaplan SL. Antibiotic therapy and acute outcome of meningitis due to *Streptococcus pneumoniae* considered intermediately susceptible to broad-spectrum cephalosporins. *Antimicrob Agents Chemother* 1994; 38:918–923.
61. Viladrich P, Gudiol F, Liñares J, Rufí G, Ariza X, Pallarés R. Evaluation of vancomycin in the therapy of adult pneumococcal meningitis. *Antimicrob Agents Chemother* 1991; 35:2467–2472.
62. Paris M, Hickey SM, Uscher MI, Shelton S, Olsen KD, McCracken GH Jr. Effect of dexamethasone on therapy of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis. *Antimicrob Agents Chemother* 1994; 38:1320–1324.
63. Cabellos C, Martínez-Lacasa J, Martos A, et al. Influence of dexamethasone on efficacy of ceftriaxone and vancomycin therapy in experimental pneumococcal meningitis. *Antimicrob Agents Chemother* 1995; 39:2158–2160.
64. Friedland IR, McCracken GH. Management of infections caused by antibiotic-resistant *Streptococcus pneumoniae*. *N Engl J Med* 1994; 331:377–382.
65. Paris MM, Ramilo O, McCracken GH. Management of meningitis caused by penicillin-resistant *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 1995; 39:2171–2175.
66. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. *N Engl J Med* 1997; 336:708–716.
67. Kaplan SL. Management of pneumococcal meningitis. *Pediatr Infect Dis J* 2002; 21: 589–591.
68. Fenoll A, Asensio G, Jado I, et al. Antimicrobial susceptibility and pneumococcal serotypes. *J Antimicrob Chemother* 2002; 50(suppl. C):13–20.
69. Oteo J, Cruchaga S, Campos J, et al. Resistencia a antibióticos en 622 *Streptococcus pneumoniae* aislados de líquido cefalorraquídeo y sangre en 33 hospitales españoles de la Red Europea de Vigilancia de Resistencia de Antibióticos (2000). *Enferm Infecc Microbiol Clín* 2003; 21:12–19.
70. Friedland IR, Klugman KP. Cerebrospinal fluid bactericidal activity against cephalosporin-resistant *Streptococcus pneumoniae* in children with meningitis treated with high-dosage cefotaxime. *Antimicrob Agents Chemother* 1997; 41:1888–1891.
71. Friedland IR, Paris M, Shelton S, McCracken Jr. Time-kill studies of antibiotic combinations against penicillin-resistant and -susceptible *Streptococcus pneumoniae*. *J Antimicrob Chemother* 1994; 43:231–237.
72. Friedland IR, Paris M, Ehrett S, Hickey S, Olsen KD, McCracken GH. Evaluation of antimicrobial regimens for treatment of experimental penicillin and cephalosporin resistant pneumococcal meningitis. *Antimicrob Agents Chemother* 1993; 37:1630–1636.

73. Klugman KP, Friedland IR, Bradley JS. Bactericidal activity against cephalosporin-resistant *Streptococcus pneumoniae* in cerebrospinal fluid of children with acute bacterial meningitis. *Antimicrob Agents Chemother* 1995; 39:1989–1992.
74. Doit CP, Bonacorsi SP, Fremaux AJ, et al. In vitro killing activities of antibiotics at clinically achievable concentrations in cerebrospinal fluid against penicillin-resistant *Streptococcus pneumoniae* isolated from children with meningitis. *Antimicrob Agents Chemother* 1994; 38:2655–2659.
75. Tubau F, Liñares J, Ardanuy C, et al. Actividad bactericida in vitro de diferentes combinaciones de antibióticos frente a *Streptococcus pneumoniae* resistente a penicilina y cefotaxima. *Enferm Infecc Microbiol Clin* 1996; 14:590–595.
76. Fiore AE, Moroney JF, Farley MM, et al. Clinical outcomes of meningitis caused by *Streptococcus pneumoniae* in the era of antibiotic resistance. *Clin Infect Dis* 2000; 30:71–77.
77. Kellner JD, Scheifele DW, Halperin SA, et al. Outcome of penicillin-nonsusceptible *Streptococcus pneumoniae* meningitis: a nested case-control study. *Pediatr Infect Dis J* 2002; 21:903–910.
78. Liñares J, Pérez JL, Garau J, Murgui L, Martin R. Comparative susceptibilities of penicillin-resistant pneumococci to co-trimoxazole, vancomycin, rifampin, and 14 β -lactam antibiotics. *J Antimicrob Chemother* 1984; 13:353–359.
79. Fenoll A, Jado I, Vicioso D, Pérez A, Casal J. Evolution of *Streptococcus pneumoniae* serotypes and antibiotic resistance in Spain: update (1990–1996). *J Clin Microbiol* 1998; 36:3447–3454.
80. Whitney CG, Farley MM, Hadler J, et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in United States. *N Engl J Med* 2000; 343:1917–1924.
81. Nahata MC, Fan-Havard P, Barson WJ, Bartkowski HM, Kosnic EJ. Pharmacokinetics, cerebrospinal fluid concentration, and safety of intravenous rifampin in pediatric patients undergoing shunt replacements. *Eur J Clin Pharmacol* 1990; 38:515–517.
82. Nau R, Wellmer A, Soto A, et al. Rifampin reduces early mortality in experimental *Streptococcus pneumoniae* meningitis. *J Infect Dis* 1999; 179:1557–1560.
83. Böttcher T, Gerber J, Wellmer A, et al. Rifampin reduces production of reactive oxygen species of cerebrospinal fluid phagocytes and hippocampal neuronal apoptosis in experimental *Streptococcus pneumoniae* meningitis. *J Infect Dis* 2000; 181:2095–2098.
84. Barakett V, Lesage D, Delisle F, Vergaz P, Petit JC. Killing kinetics of vancomycin and rifampin tested alone and in combination against penicillin-resistant *Streptococcus pneumoniae*. *Eur J Clin Microbiol Infect Dis* 1993; 12:69–71.
85. Nau R, Kaye K, Sachdeva M, Sande ER, Täuber MG. Rifampin for therapy of experimental pneumococcal meningitis in rabbits. *Antimicrob Agents Chemother* 1994; 38:1186–1189.
86. Martínez-Lacasa J, Cabellos C, Martos A, et al. Experimental study of the efficacy of vancomycin, rifampin and dexamethasone in the therapy of pneumococcal meningitis. *J Antimicrob Chemother* 2002; 49:507–513.
87. Radetsky MS, Johansen TL, Lauer BA, et al. Multiply resistant pneumococcus causing meningitis: its epidemiology within a day-care center. *Lancet* 1981; 2:771–773.
88. Viladrich PF, Tubau F, Cabellos C, et al. Vancomycin plus rifampin for therapy of adult pneumococcal meningitis. Ninth European Congress of Clinical Microbiology and Infectious Diseases; Berlin, Germany; March 21–24, 1999. Abstract P616.
89. Buzón LM, Guerrero A, Romero J, Santamaría JM, Bouza E. Penicillin-resistant *Streptococcus pneumoniae* meningitis treated with vancomycin. *Eur J Clin Microbiol* 1984; 3:442.
90. Dagan R, Velghe L, Rodda JL, Klugman KP. Penetration of meropenem into the cerebrospinal fluid of patients with inflamed meninges. *J Antimicrob Chemother* 1994; 34:497–498.
91. Fuchs PC, Barry AL, Brown SD. Pneumococcal susceptibility to meropenem. *J Antimicrob Chemother* 1996; 37:1036–1037.

92. Nau R, Schmidt T, Kaye K, Froula JL, Täuber MG. Quinolone antibiotics in therapy of experimental pneumococcal meningitis in rabbits. *Antimicrob Agents Chemother* 1995; 39:593–597.
93. Ostergaard C, Klitmoller Sorensen T, Dahl Knudsen J, Frimodt-Moller N. Evaluation of moxifloxacin, a new 8-methoxyquinolone, for treatment of meningitis caused by a penicillin-resistant pneumococcus in rabbits. *Antimicrob Agents Chemother* 1998; 42:1706–1712.
94. Shapiro M, Donovan KD, Gage JW. 2000. Comparative therapeutic efficacy of clinafloxacin in a pneumococcal meningitis mouse model. *J Antimicrob Chemother* 2000; 45:489–492.
95. Smirnov A, Wellmer A, Gerber J, Maier K, Henne S, Nau R. Gemifloxacin is effective in experimental pneumococcal meningitis. *Antimicrob Agents Chemother* 2000; 44:767–770.
96. Cottagnoud P, Acosta F, Cottagnoud M, Tauber MG. Gemifloxacin is efficacious against penicillin-resistant and quinolone-resistant pneumococci in experimental meningitis. *Antimicrob Agents Chemother* 2002; 46:1607–1609.
97. Cottagnoud P, Acosta F, Cottagnoud M, Pfister M, Tauber MG. Efficacies of BMS284756 against penicillin-sensitive, penicillin-resistant, and quinolone-resistant pneumococci in experimental meningitis. *Antimicrob Agents Chemother* 2002; 46:184–187.
98. Sáez-Llorens X, McCoig C, Feris J, et al. Quinolone treatment for pediatric bacterial meningitis: a comparative study of trovafloxacin and ceftriaxone with or without vancomycin. *Pediatr Infect Dis J* 2002; 21:14–22.
99. Chen DK, McGeer A, de Azavedo JC, Low DE. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. *N Engl J Med* 1999; 341:233–239.
100. Empey PE, Jennings HR, Thornton AC, Rapp RP, Evans ME. Levofloxacin failure in a patient with pneumococcal pneumonia. *Ann Pharmacother* 2001; 35:687–690.
101. Davidson R, Cavalcanti R, Brunton JL, et al. Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. *N Engl J Med* 2002; 346:747–750.
102. Wortmann GW, Bennett SP. Fatal meningitis due to levofloxacin-resistant *Streptococcus pneumoniae*. *Clin Infect Dis* 1999; 29:1599–1560.
103. Liñares J, De la Campa AG, Pallares R. Fluoroquinolone resistance in *Streptococcus pneumoniae*. *N Engl J Med* 2001; 341:1546–1547.
104. Cottagnoud P, Gerber CM, Acosta F, Cottagnoud M, Neftel K, Tauber MG. Linezolid against penicillin-sensitive and -resistant pneumococci in the rabbit meningitis model. *J Antimicrob Chemother* 2000; 36:1403–1413.
105. Gomez-Barreto D, Calderon-Jaimes E, Rodríguez RS, de los Monteros LE. Clinical outcome of invasive infections in children caused by highly penicillin-resistant *Streptococcus pneumoniae* compared with infections caused by penicillin-susceptible strains. *Arch Med Res* 2000; 31:592–598.
106. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanent Vaccine Study Center Group. *Pediatr Infect Dis J* 2000; 19:187–195.
107. Dagan R, Fraser D. Conjugate pneumococcal vaccine and antibiotic-resistant *Streptococcus pneumoniae*: herd immunity and reduction of otitis morbidity. *Pediatr Infect Dis J* 2000; 19:S79–S88.
108. Pai VB, Heyneman CA, Erramouspe J. Conjugated heptavalent pneumococcal vaccine. *Ann Pharmacother* 2002; 36:1403–1413.
109. Viladrich PF, Cabellos C, Martos A, Martinez Lacasa JT, Gudiol F. Lack of efficacy of pneumococcal vaccine in preventing pneumococcal meningitis due to cerebrospinal fluid leaks. 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); Anaheim, CA; October 11–14, 1992. Abstract 1282.

<http://www.springer.com/978-1-58829-230-8>

Management of Multiple Drug-Resistant Infections

Gillespie, S.H. (Ed.)

2004, XII, 403 p. 11 illus., Hardcover

ISBN: 978-1-58829-230-8

A product of Humana Press