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# ***Streptococcus pneumoniae* as an agent of nosocomial infection: treatment in the era of penicillin-resistant strains**

F. Paradisi, G. Corti and R. Cinelli

Infectious Disease Unit, University of Florence School of Medicine, Florence, Italy

*Streptococcus pneumoniae* is a well-known agent of community-acquired infections such as sinusitis, otitis media, pneumonia, bacterial meningitis, bacteremia and acute exacerbations of chronic bronchitis. However, the role of *S. pneumoniae* as a cause of nosocomial infections of respiratory tract, bloodstream and central nervous system is more and more recognized, primarily in high-risk patients with depression of their immune function. Therapy of pneumococcal infections is made difficult by the emergence and spread of bacterial resistance to penicillin and other  $\beta$ -lactams as well as to a number of antimicrobials such as macrolides, chloramphenicol, tetracyclines and sulfonamides. This epidemiological situation is a cause for concern world-wide, but it primarily affects some European countries, North America, South Africa and the Far East. The main consequence on therapeutic grounds is that in severe infections such as bacterial meningitis, the addition of vancomycin to a third-generation cephalosporin is advisable while awaiting laboratory test results, even in areas with low prevalence of penicillin-resistant pneumococci. However, a  $\beta$ -lactam agent can also be a valid choice in the presence of potentially lethal infections such as pneumonia or in the case of penicillin intermediately resistant isolates. In recent years, new alternative molecules have been introduced into clinical practice for therapy of infections caused by penicillin-resistant pneumococci. In both in vivo and in vitro studies, drugs of the classes of fluoroquinolones (levofloxacin, moxifloxacin, gatifloxacin), streptogramins (quinupristin/dalfopristin) and oxazolidinones (linezolid) have shown good microbiologic and clinical efficacy against penicillin-resistant pneumococci. In this era of world-wide spread of penicillin-resistant pneumococci, use of polysaccharide or conjugated vaccines is highly recommended.

**Keywords** nosocomial infection, *Streptococcus pneumoniae*, penicillin resistance, multiantibiotic resistance, antibiotic therapy,  $\beta$ -lactams, fluoroquinolones, streptogramins, oxazolidinones

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## **INTRODUCTION**

*Streptococcus pneumoniae* is a Gram-positive coccus, surrounded by a polysaccharide capsule that allows the micro-organism to avoid phagocytosis, representing a major virulence factor; moreover, capsular variability permits different subtypes to avoid immune detection by antibodies previously generated by infection or administration of vaccine. Some capsular types are less immunogenic and therefore associated with prolonged asymptomatic carrier status. The ability to adhere to mucosal linings is another important virulence factor [1].

*Streptococcus pneumoniae* is a major and well-known cause of community-acquired infections. It is the most prevalent agent of acute sinusitis, acute otitis media, pneumonia and bacterial meningitis, accounting for 30%–50% of each syndrome, and it is also the second cause of bacteremia and of acute exacerbation of chronic obstructive pulmonary disease, accounting for approximately 22% of cases [2–14]. Moreover, *S. pneumoniae* is a frequent cause of both morbidity and mortality; it has been estimated that about 500 000 cases of pneumonia, 55 000 cases of bacteremia and 6000 cases of meningitis are caused by pneumococci annually in the USA, with a mortality range from <1% to >50% [15]. Although seen infrequently today, unusual manifestations of invasive pneumococcal infections such as pancreatic and liver abscesses, aortitis, gingival lesions, phlegmonous gastritis, inguinal adenitis, testicular and tubo-ovarian abscesses and necrotizing fasciitis are reported. These clinical entities occur especially in

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Corresponding author and reprint requests: G. Corti, Infectious Disease Unit, University of Florence School of Medicine, Careggi Hospital, Viale G.B. Morgagni 85, I-50134 Florence, Italy  
Tel.: +39 55 427 9484  
Fax: +39 55 427 9480  
E-mail: cortig@ao-careggi.toscana.it

the presence of some risk factors such as alcoholism, human immunodeficiency virus (HIV) infection, splenectomy, connective tissue diseases, steroid use, diabetes mellitus and intravenous drug abuse [16].

Nosocomial infection is defined by the isolation of a pathogen from a previously sterile body site more than 48–72 h after admission to the hospital. *Streptococcus pneumoniae* was recognized as a common cause of hospital-acquired infections before the introduction of penicillin into clinical practice [17,18], but now it seems to be less frequent, being responsible for 4% of nosocomial acute sinusitis, 5% of bacterial meningitis, 2% of bacteremias and a low percentage of pneumonias (i.e. an incidence of 0.03 bacteremic pneumonias per 1000 patient-days during the years 1989–93) [13,19–22]. Nevertheless, *S. pneumoniae* is being increasingly recognized as a nosocomial pathogen in some subgroups of patients, such as the elderly, oncologic subjects and patients with ultimately fatal diseases. Indeed, in elderly patients up to 20% of hospital-acquired pneumonia is due to *S. pneumoniae* [2,23,24], although some authors have reported much greater rates of incidence, i.e. 38% [25]. Bartlett *et al* reported a 26% incidence of nosocomial pneumococcal pneumonia, with a 19% mortality rate [26]. Although pneumococcal bacteremia is more frequent in HIV-infected patients (9.4 cases/1000 population per year), they have the same or even a significantly lower mortality from pneumococcal pneumonia than HIV-negative subjects do, probably because of their relative youth [22]. Up to 41% of nosocomial bacteremias in elderly patients with serious underlying diseases are caused by pneumococci. The statistically significant risk factors in patients with nosocomial pneumococcal bacteremia are poor functional status, malignant neoplasm, ultimately fatal underlying disease, previous administration of antibiotics, and presence of shock, with a 74% overall mortality rate. Mortality directly related to pneumococcal bacteremia is 52%, being not significantly different from the mortality rate for community-acquired pneumococcal bacteremia (39%) [27]. Other authors report a 58.7% incidence of pneumococcal nosocomial bacteremia in elderly patients with some predisposing factors: previous administration of antipneumococcal antimicrobial or psychotropic agents, lower respiratory tract manipulation and ultimately fatal underlying diseases, with a 59.5% mortality [28].

Either sporadic cases or epidemics may derive from horizontal spread of *S. pneumoniae* in the hospital. Serological typing and antibiotic susceptibility profiles are not sufficiently discriminatory, so DNA fingerprinting by polymerase chain reaction (PCR) and pulsed-field gel electrophoresis (PFGE) typing are now mandatory [2].

Nosocomial epidemics of pneumococcal infection can occur as well, primarily in elderly patients. The infecting pneumococcal strain may originate from the patient's upper

respiratory tract flora, and may have been acquired before or after admission to hospital, from a transient asymptomatic carrier, or from a pneumococcal disease [24,29].

## NOSOCOMIAL INFECTION

An outbreak of infection with serotype 3 *S. pneumoniae* occurred in a male geriatric ward during November 1984; the index case was an 81-year-old man with a fractured femur, who developed a chest infection and expectorated frequently and carelessly. Within 2 weeks, four more patients developed symptoms of chest infection associated with type 3 *S. pneumoniae* in their sputum; one of these patients died, and all were in close proximity to the index case. A cluster of three infections occurred in a female geriatric ward during December 1984 [25].

Another outbreak of pneumococcal respiratory infection with a presumed route of spreading from patient to patient was reported in an adult oncology unit in 1991; eight patients developed clinical evidence of pneumonia over an 11-day period, and two severely ill patients with diffused metastatic infiltrates died. All pneumococcal isolates belonged to the serotype 14 and all patients had evidence of pneumonia [30]. Cartmill *et al* reported an outbreak of nosocomial chest infection occurring in an acute geriatric ward of a UK hospital during the same year. Three patients developed pneumonia; the index case was a nose and throat pneumococcal carrier. The outbreak strain was serotype 6. No patient died [31].

In 1992 an outbreak of *S. pneumoniae* type 9 infection was described in a British acute medical ward; four elderly subjects had pneumonia and three had septicaemia, one of whom died [32]. A year later, in another British hospital for the elderly, 10 respiratory and bloodstream infections were observed, eight of which were hospital-acquired and due to *S. pneumoniae* type 9. This outbreak was probably favoured by the fact that the index case remained unrecognized for more than 2 weeks and was treated with antibiotics without knowing the *in vitro* susceptibility profile; indeed, the strain was resistant to penicillin and trimethoprim [33].

Nosocomial pneumococcal infections are reported to occur in the intensive care unit (ICU), although less frequently in comparison with infections due to other micro-organisms such as enterobacteriaceae and staphylococci. In particular, *S. pneumoniae* is responsible for 5%–20% of early onset ventilator-associated pneumonia (VAP), which occurs during the first 4 days of the hospital stay. Aspiration appears to be the major route for the entry of bacteria into the lower respiratory tract, although host factors, oropharyngeal colonization, cross-infections and the use of nasogastric and endotracheal tubes all increase the risk of developing a bacterial VAP [34].

Dhillon *et al* reported a case of central venous catheter-related bacteremia due to *S. pneumoniae* in a 41-year-old

woman with schizophrenia, seizure disorder, Graves' disease, abdominal pain and vomiting. She had a femoral triple-lumen catheter inserted for total parenteral nutrition. Two sets of blood cultures grew *S. pneumoniae* and the tip of the triple-lumen catheter grew more than 300 colony-forming units (CFU) of *S. pneumoniae* by the roll-plate technique. A colony count greater than 15 on blood-agar plate is considered significant and indicates that the catheter is the source of bacteremia. Other authors have reported cases of pneumococcal colonization of central venous catheters, or have cultured *S. pneumoniae* from the tip of central venous catheters or from the port pocket infection of an implanted infusion port device, but this was not associated with bacteremia [35].

Nosocomial pneumococcal outbreaks are reported in pediatric ICUs as well: an 11-month-old girl suffered from a febrile pneumonia and developed acute meningitis 15 days later. Culture of cerebrospinal fluid (CSF) grew *S. pneumoniae* serotype 23F. She died the day after. Five days later, a 5-month-old infant hospitalized in the next bed developed an acute pulmonary infection due to the same strain; randomly amplified polymorphic DNA analysis showed an identical profile of both strains [36]. A very unusual route for transmission was suggested by Methar and coworkers, who reported the isolation of *S. pneumoniae* type 6 in two neonates resuscitated consecutively with the same piece of equipment 48 h apart [37].

## ANTIBIOTIC RESISTANCE

Pneumococci have been among the most highly penicillin-susceptible bacteria throughout the first quarter-century of penicillin use. The first clinical penicillin-resistant pneumococcal (PRP) strain was isolated in 1967 from a patient in Papua, New Guinea. Between 1967 and 1977, sporadic reports on PRP clinical strains from various parts of the world were published. The next dramatic event in the epidemiology of antibiotic-resistant pneumococci was the outbreak of pneumococcal disease caused by multiresistant strains in South African hospitals in 1977. In contrast to the first isolate, which remained still susceptible to chloramphenicol, tetracycline, erythromycin and sulfonamides, the South African strains were shown to have greatly increased minimal inhibitory concentrations (MIC) not only for penicillin, but also for many other drugs [38]. The US National Committee for Clinical Laboratory Standards has defined pneumococcal susceptibility to penicillin as an MIC less than 0.125 µg/mL, intermediate susceptibility as an MIC between 0.125 and 1 µg/mL, and resistance as an MIC more than 1 µg/mL; strains showing MIC > 2 µg/mL are defined as highly resistant [39]. Penicillin resistance is due to stepwise alterations in pneumococcal molecular targets for β-lactams; in other words, the high-

molecular-weight penicillin-binding proteins (PBPs) involved in the synthesis of the bacterial cell wall. Mutations in PBP2b and even in PBP1a are important for the development of high-level penicillin resistance, whereas mutations in PBP2x and PBP3 are responsible for the development of resistance to cephalosporins [40]. Indeed, PBPs from penicillin-resistant clones have radically reduced affinities and/or binding capacities for the antibiotic molecule. High-level resistance to penicillin involves gradual remodelling of several (almost three to four) PBPs in parallel with the stepwise increase in resistance level. Cloning and sequencing of resistant PBP genes identified mosaic sequences in each one of these, indicating that the origin of these PBP genes must have been heterologous recombination events in which nonpneumococcal bacteria, such as *Streptococcus mitis*, have served as DNA donors. The process by which pneumococci acquire the heterologous DNA sequences involves the unique capacity of this species for recognizing, absorbing and integrating extracellular polydeoxynucleotides through the process of competence for genetic transformation. Acquisition of these DNA sequences may occur in a stepwise manner; incorporation of one of such altered low-affinity PBP genes marks the beginning of a resistant clone, which then expands by cell division until one member of this lineage engages in a second recombinational event, which results in another modification in a second PBP gene. The progeny of such a cell, which now has an increased penicillin MIC, may undergo further recombination events, each of those increasing the resistance level. Moreover, multiresistant pneumococci are capable of undergoing spontaneous capsular switch, which is another issue of particular concern because of the presence of a setting characterized by the selective pressure exerted by vaccines [38,41]. Thus, in the evolution of PRP populations, several evolutionary phases could be distinguished: the susceptible phase, where essentially a single susceptible population is detectable; the early phase, where other populations begin to appear, presenting only small increases in MIC values; the low-level resistance phase, with an increase in the number of strains belonging to the 0.06–0.12 µg/mL inhibited populations, but with the appearance of some populations showing MICs 0.25–0.5 µg/mL or even 1–2 µg/mL; the multi-population phase, where the susceptible population decreases, the low-level population remains, and there is a great increase in the population inhibited by MICs of 1–2 µg/mL; the high-level resistance phase, with a clear decrease in low-level resistant populations and a great increase in strains inhibited by MICs of 1–4 µg/mL [42].

Analyses by molecular techniques have shown large variations in the features of PRP on the basis of their MIC for penicillin: isolates with low-level penicillin resistance (MIC = 0.125–0.25 µg/mL) belong to multiple serotypes and

are infrequently resistant to multiple antibiotics; strains with MICs of 1–2 µg/mL show a sharp reduction in both serotype distribution and variation of genetic background; isolates with even higher MICs carry multiresistance patterns and belong to few serotypes. These latter are generally 6, 9, 14, 19 and 23, the so-called ‘pediatric’ capsular types, being most frequently isolated in children. Bacterial resistance seems to be more prevalent among these serotypes and the hypothesis that PRP originate in children and then spread to adults has been posed [40].

When PRP strains were initially isolated from the upper respiratory tract of children in US communities, they tended to be equally divided between relatively resistant and highly resistant organisms; in contrast, European studies have shown rates of relatively resistant strains 2–3-fold greater than highly resistant strains. A trend similar to the European pattern now appears to be occurring in the USA. The risk of being infected or colonized with a PRP strain is significantly higher in younger children or in those who have received multiple courses of antibiotics; the reasons potentially related to the high prevalence of resistant strains among children could be the frequent inappropriate use of antibiotics for viral infections of the upper respiratory tract, the selection of antibiotics with inadequate coverage, the long-term use of antibiotics for chemoprophylaxis, and noncompliance with the prescribed therapy [12]. Indeed, in Europe the highest PRP prevalence is reported in France and Spain where antibiotics are widely prescribed and patients’ compliance with at least 50% of oral antimicrobial prescriptions is inadequate [43]. The likelihood of isolating a potentially resistant pathogen decreases with increasing age; in Eastern and Central Europe, the prevalence of PRP falls from 73% to 40% as the patient’s age rises from under 12 to over 60 months [44].

By multivariate analysis, an age of less than 2 years, living in an area with high antimicrobial consumption, and individual use of antimicrobials significantly influenced the likelihood of carrying a penicillin-nonsusceptible pneumococcal (PNSP) strain; by univariate analysis, recent (2–7 weeks before) antimicrobial use and use of cotrimoxazole were also significantly associated with carriage of PNSP strains [45]. The French experience underscores that the main risk factor for carrying a PNSP strain is recent β-lactam use [46]. Greenberg and Martin report a 53% prevalence rate of PNSP carriage in healthy children attending a day-care centre in western Kentucky [47]. Keuleyan *et al* report 22.4% rates of PNSP carriage among healthy children in Bulgaria, and a statistically significant percentage of children with PNSP had received antibiotic therapy during the previous 3 months [48], thus intervention to reduce high antimicrobial administration is believed to be effective in reducing the prevalence of PNSP carriers, as in the Icelandic approach [49,50].

Serotyping of pneumococcal isolates during the last decade in Spain has revealed that penicillin-resistant serotypes are the

common ones to be found in the population, mainly serotypes 6, 9, 14, 15, 19 and 23, whereas serotypes 10, 11 and 33 show only a very low rate of penicillin resistance [51].

The rate of PNSP varies by virtue of the source of the specimens as well, middle ear fluid, CSF and lower respiratory tract having the greatest prevalence rates (18%, 10% and 10%, respectively). Risk factors for infections with PNSP identified by a logistic regression model are under 15 years of age, isolation of the micro-organism from the upper respiratory tract, HIV coinfection, β-lactam use in the previous 6 months, nosocomial acquisition, hospitalization during the previous 3 months, and episodes of pneumonia during the previous year; nosocomial acquisition is a risk factor associated with both invasive and noninvasive strains [52]. Similar risk factors have been identified in other studies [53–56].

The epidemiological situation of PRP is a cause for concern world-wide (Table 1) [57]; results of the Alexander Project show that among European countries Spain and France have the highest prevalence of PNSP: both intermediate (MIC 0.12–1 µg/mL) and resistant (MIC ≥ 2 µg/mL) phenotypes are present, with combined rates of more than 50%. PNSP percentages in excess of 20% are found in Ireland, Portugal, the Slovak Republic and Hungary. Penicillin resistance continues to evolve in the USA, with combined rates of 18.6%. Prevalence rates are high in Mexico and Hong Kong (55.5%). Macrolide resistance is increasing generally among both penicillin-susceptible and penicillin-resistant strains, with variations between countries; overall, the percentage of pneumococcal strains that are resistant to macrolides exceeds the percentage of PRP: in 1997, 21.9% of all pneumococcal isolates were resistant to macrolides, compared with 14.1% that were resistant to penicillin [58]. An age of under 5 years and nosocomial acquisition of the strain constitute risk factors for macrolide resistance [54].

**Table 1** World-wide prevalence of penicillin-resistant pneumococci

Low (<10%)	Intermediate (10%–30%)	High (>30%)
Italy	Ireland	France
Germany	Portugal	Spain
UK	Hungary	Slovak Republic
Switzerland	Canada	Bulgaria
Benelux	Argentina	Romania
Scandinavia	Brazil	Turkey
North Africa	Israel	USA
Peru	Saudi Arabia	Mexico
New Zealand	Kenya	South Africa
	Nigeria	Thailand
	Philippines	Japan
	Singapore	South Korea
	Australia	Taiwan
		Hong Kong
		Vietnam

Data from the SENTRY Antimicrobial Surveillance Program in North America show combined rates of PNSP of 27.8% in the USA and 16% in Canada during 1997; the worrisome data are the increasing resistance to other  $\beta$ -lactams, including amoxicillin (18.1%), cefaclor (10.5%), cefuroxime (19.5%), cefepime (8.2%) and cefotaxime (4%). Most of these strains show multiantibiotic resistance [59]. The same author had reported resistance rates of 23.6% to penicillin, 3%, 5% and 12% to cefotaxime, ceftriaxone and cefuroxime, respectively, 10% to macrolides, 4.3% to chloramphenicol, 7.5% to tetracycline and 18% to cotrimoxazole during the winter months of 1994 and 1995 [60]. Schito *et al* report a 10.2% prevalence rate of PNSP in Italy in 1999, with high-level resistance accounting for only 4.1% [61,62]. Although in the presence of high prevalence rates of multiantibiotic resistance among *S. pneumoniae* there is no resistance to vancomycin and teicoplanin, and also levofloxacin continues to maintain a high level of activity against multiresistant pneumococci, in Asia and Europe, levofloxacin resistance has been detected in only 0.9% of strains isolated in Japan, 0.8% of strains from China, 0.4% of strains from Germany and none of the strains from Italy, France, Spain and the UK [63]. In Asia, Korea has the greatest frequency of PNSP (79.7%), followed by Japan (65.3%), Vietnam (60.8%), Thailand (57.9%), Taiwan (38.7%) and Singapore (23.1%); various proportions of the PNSP strains also show resistance to cephalosporins, chloramphenicol, macrolides and ciprofloxacin, but none is resistant to glycopeptides. These high prevalence rates of multiantibiotic resistance are partly explained by the injudicious use of antibiotics by medical personnel (almost 75% of private practitioners prescribe antibiotics for aspecific infections of the upper respiratory tract), and partly by the policy of selling all kinds of antibiotics in pharmacies without any regulation [64,65]. The proportion of isolates that are not susceptible to imipenem increased during 1992–94, although resistance to imipenem remains uncommon in the USA (i.e. less than 0.5%) [66].

Nosocomial pneumococcal isolates are almost always multiresistant. De Galan *et al* report an outbreak of infection with multiresistant *S. pneumoniae* in the Netherlands; nosocomial transmission was confirmed by typing of bacterial isolates, which shared the same genotype and serotype and displayed overlapping drug-resistance profiles [67]. Gillespie and colleagues have documented an outbreak of penicillin-resistant *S. pneumoniae* in a health care centre for the elderly and demonstrated, using a simple PCR-based genotyping method for the PBP genes 1a, 2x and 2b, that the nine patients were all infected by *S. pneumoniae* serotype 9S, which had altered those PBPs, a pattern clearly distinguishable from other penicillin-resistant strains isolated in the same centre. Four patients died but only two deaths were directly attributable to the

pneumococcal infection [68]. Cimolai and coworkers report on two patients who were found to harbour intermediate-level penicillin-resistant *S. pneumoniae* in a pediatric hospital setting. For the first patient, the micro-organism was isolated from a tracheal aspirate, and for the second one, a positive blood culture was found a short time after the index case. Two molecular typing techniques (enterobacterial repetitive intergenic consensus sequence PCR and repetitive sequence-based PCR) demonstrated homology among these isolates, which confirmed interpersonal spread [69]. Gould *et al* report the case of six patients colonized with a multiresistant strain of *S. pneumoniae* [70]. Pallares *et al* point out the case of three patients with nosocomial pneumonia due to PRP with an identical sensitivity pattern and serotype 19 while they were hospitalized in the same ward [55].

Thus, nosocomial acquisition of infection is one of the many risk factors that in univariate and logistic regression analyses are significantly associated with PRP infections, along with pediatric age, previous hospitalization and previous  $\beta$ -lactam therapy [52,55,65]. In the case of erythromycin-resistant *S. pneumoniae*, only an age < 5 years and nosocomial acquisition have been found to be independent risk factors [54]. Nosocomial acquisition of infection along with advanced age and the presence of severe underlying conditions or complications are risk factors significantly associated with higher mortality from pneumococcal disease. Surprisingly, recent studies have not found penicillin resistance to be related significantly to clinical course or mortality [22,71], in contrast with a former study in which the overall mortality rate was significantly higher in patients with PRP bacteremic pneumonia (54% vs. 25%,  $P = 0.03$ ) than in subjects with penicillin-sensitive strains [55].

## ANTIBIOTIC TREATMENT

The emergence of PRP and, in concert, multiantibiotic resistant *S. pneumoniae* represents the pre-eminent challenge to the successful treatment of pneumococcal infections, especially in the case of nosocomial infections, in which the patients' underlying conditions and the prompt institution of an appropriate therapy may markedly influence the outcome.

Acute otitis media (AOM) is generally a mild disease, but it can become chronic or lead to hearing loss, mastoiditis and severe intracranial complications, thus antibiotics are almost invariably prescribed. There is a lot of confusion about the optimal management of AOM. There are two conditions an antimicrobial drug has to meet for effective treatment of AOM: the first is being active against the causative micro-organism, the second is achieving appropriate concentrations in the middle ear fluid (MEF). It has been calculated that an 80%–85% successful outcome of AOM therapy is achieved

when the MEF concentration of the drug exceeds the MIC<sub>90</sub> for at least 40%–50% of the dosing interval. In general, oral cephalosporins possess good microbiologic activity and reach MEF concentrations that are 25%–60% of serum concentrations. Amoxicillin demonstrates a similar pattern, whether or not associated with clavulanic acid, and even the new macrolides clarithromycin and, especially, azithromycin and cotrimoxazole achieve MEF concentrations higher than serum concentrations. Typically, the therapy of AOM consists of administration of an oral agent. The duration of treatment is 10 days, although shorter schedules can be given, i.e. 3- or 5-day azithromycin or a single intramuscular dose of ceftriaxone. At any rate, oral amoxicillin should remain the first-line antimicrobial agent for treating AOM. In view of the increasing prevalence of PNSP, the safety of amoxicillin at higher than standard dosages and evidence that higher dosages of the drug can achieve effective MEF concentrations, an increase in the dosages used for empiric treatment from 40 to 45 mg/kg/day to 80–90 mg/kg/day is recommended. For patients with clinically defined treatment failure after 3 days of therapy, useful alternatives include oral amoxicillin/clavulanate, cefuroxime axetil or intramuscular ceftriaxone [72–74].

In the evaluation of therapy, an important parameter to be considered is the therapeutic index, defined as the ratio of drug concentration achievable at the site of infection and the MIC. In the case of meningitis, the relevant parameter is the minimal bactericidal concentration (MBC), and it has been suggested that for penicillin and most other  $\beta$ -lactams, the therapeutic index should be 10-fold or higher. Moreover, the bactericidal activity and efficacy of  $\beta$ -lactams are dependent on the time for which their concentration exceeds the MIC, which should be at least 40%–50% of the dosing interval. The levels of penicillin achieved in the CSF are close to or even lower than the MICs of intermediately resistant strains, and this explains the number of therapeutic failures. When infection is located outside the central nervous system, resistance to penicillin is not associated with poor outcome; it can be explained by the fact that levels of  $\beta$ -lactams achievable in serum and lung tissues are several times higher than the MICs for the most common currently infecting pneumococcal strains. However, it is important to remember that there are several cephalosporins such as ceftazidime, cefaclor, or cefixime with very poor in vitro activity against PNSP; thus, these drugs must not be used in treating pneumococcal infections [75].

Currently, it seems prudent to treat all pediatric and adult patients with purulent meningitis empirically, with vancomycin (30 mg/kg/day) combined with either cefotaxime or ceftriaxone (high doses) while awaiting CSF culture with antimicrobial susceptibility test results, as the association shows synergistic effect; this approach seems to be appropriate even if the prevalence of penicillin and cephalosporin-resistant

pneumococci is <10% or unknown in a specific area, because of therapeutic failures reported in the case of treatment with cephalosporins alone and because the patient may have a poor outcome if not managed aggressively from the start. Alternative regimens for initial empirical therapy are the combination of vancomycin and rifampin (900 mg/day) or meropenem, the use of imipenem being limited by its propensity to cause seizures. Standard doses of intravenous penicillin G remain the therapy of choice for patients having susceptible strains. Newer quinolones are active against *S. pneumoniae*, including penicillin- and cephalosporin-resistant strains, and can represent good alternatives for treating bacterial meningitis [75–77].

The serum concentrations of penicillin and other  $\beta$ -lactams achievable with intravenous therapy are many times greater than the MIC for pneumococci with intermediate penicillin resistance and even for many highly penicillin-resistant strains. As a result, it is likely that patients with sepsis caused by PNSP will respond to these drugs, although for patients in whom infections caused by high-level PRP are suspected, such as nosocomial infections in debilitated subjects, it is advisable to use other agents such as glycopeptides or carbapenems [78].

Patients with pneumonia have to be treated empirically since laboratory testing requires at least 24–48 h before the results are known; moreover, despite extensive diagnostic testing, a causative agent is identified in only about 50% of all cases of pneumonia. Therapy of presumptive pneumococcal pneumonia should be initially chosen in each patient according to the severity of the infection. In outpatients for whom the pneumococcal etiology is strongly suggested by clinical and radiological findings and in areas where PRP are not significantly prevalent, high dosage of oral amoxicillin (50 mg/kg/day) may be the therapy of choice; other oral alternatives could be amoxicillin/clavulanate (1 g every 8 h), doxycycline (100 mg every 12 h) and oral cephalosporins. In patients with severe pneumonia or hospital-acquired pneumonia and in areas with high prevalence of PRP, the initial antibiotic coverage must include intravenous ceftriaxone (1–2 g/day), cefotaxime (1–2 g every 8 h), amoxicillin/clavulanate (2.2 g every 8 h), carbapenems (imipenem 500 mg every 6 h, meropenem 1 g every 8 h) or newer quinolones (see below). When a pattern of antimicrobial susceptibility is available, therapy can be switched to the narrowest-spectrum antibiotic according to the susceptibility profile. Once more, penicillin G remains the treatment of choice for pneumonia and bacteremia caused by susceptible strains of *S. pneumoniae*, although it is prudent to suggest high dosages (200 000 U/kg per day) in order to achieve the highest lung and serum levels [75,79]. Even for intermediately susceptible isolates of *S. pneumoniae*, penicillin and its derivatives are still effective [80].

Fortunately, in recent years we have witnessed the introduction of new antibiotics into clinical practice with

enhanced activity against Gram-positive cocci, including PRP. The antibacterial activity of quinolones launched more than 10 years ago is generally greater against Gram-negative organisms than Gram-positive ones. This is the result of a structure-activity relationship, so that an alkylated pyrrolidine, a piperazine- or an azabicyclo-substitution at C7 had significantly improved activity against Gram-positive bacteria. Thus, newer quinolones such as clinafloxacin, gatifloxacin, gemifloxacin grepafloxacin, levofloxacin, moxifloxacin, sparfloxacin and trovafloxacin can offer therapeutic alternatives to the currently available regimens to treat infections due to multiresistant *S. pneumoniae*. In particular, available data show that moxifloxacin and trovafloxacin, and by one to four dilution steps less active gatifloxacin and grepafloxacin, exhibit a pronounced activity against *S. pneumoniae*, independently from the penicillin susceptibility profile [81]. Among the most recent quinolones, Rittenhouse and colleagues and Jorgensen and coworkers found gemifloxacin to be more potent than clinafloxacin, gatifloxacin, grepafloxacin, levofloxacin, trovafloxacin, ciprofloxacin and ofloxacin against pneumococci [82,83], whereas Perry reports that in in vitro pharmacokinetic models simulating human kinetics following oral administration, gatifloxacin showed extensive killing of pneumococci at 400 mg once-daily dose, with a postantibiotic effect of 0.5–4.8 h against penicillin-susceptible, intermediate and resistant strains [84].

The most common adverse effects of quinolones involve the gastrointestinal tract, skin, tendons and central nervous system, and they are generally mild and reversible [85]. However, postmarketing surveillance has revealed important toxicity with some molecules, such as hepatotoxicity (trovafloxacin), phototoxicity (sparfloxacin) and a significant prolongation of the QT interval (grepafloxacin, sparfloxacin), so that the use of these drugs has been strongly limited or even withdrawn.

Other new antimicrobial agents seem to be promising for treatment of PNSP infections; the streptogramin class has shown excellent activity against multiresistant Gram-positive cocci. The first agent is a water-soluble combination of quinupristin and dalfopristin in a 30/70 ratio that produces an interruption of protein synthesis. Each component is bacteriostatic, but the combination is bactericidal. Quinupristin/dalfopristin is active in vitro against most Gram-positive bacteria (except for *Enterococcus faecalis*, which is resistant) with MIC < 1 mg/L, and its activity is not modified in the case of resistance to other antimicrobials [86]. Manzor *et al* have found MICs for quinupristin/dalfopristin of 0.5 mg/L for both penicillin-susceptible and penicillin-resistant strains of pneumococci [87]. Moreover, quinupristin/dalfopristin shows a prolonged postantibiotic effect against Gram-positive bacteria (from 2 to 8 h after 1 h of exposition at concentrations of 2–4-fold the MIC values) [88].

Linezolid, a new antibiotic belonging to the class of oxazolidinones, a class of synthetic antimicrobials unrelated to any other currently available agents, is an important option for treating both community- and hospital-acquired infections due to multiresistant Gram-positive cocci. Linezolid selectively binds to the 50S ribosomal subunit near the interface with the 30S subunit. This results in a distortion that inhibits the formation of the initiation complex constructed with 30S ribosomes, mRNA, initiation factors IF1 and IF2, and fMet-tRNA. It does not inhibit the peptide elongation phase, so that this drug is generally believed to be bacteriostatic. Concentration-dependent killing has been described for some species, especially streptococci. Because of its mechanism of action, linezolid does not exhibit cross-resistance with other antimicrobials. It can be administered both orally and parenterally and, despite the lack of in vitro bactericidal activity, in some phase II trials it has been effective in treating infections due to multiresistant Gram-positive cocci [89]. Mason *et al* found that the MICs at which 90% of *S. pneumoniae* isolates tested were inhibited, were 1 mg/L for both penicillin-intermediately susceptible and -resistant strains [90].

## ANTIPNEUMOCOCCAL VACCINATION

In this era of pandemic world-wide spread of PNSP, prevention of infections by vaccination is recommended. Pneumococcal polysaccharide vaccine is safe and effective in preventing invasive infections among immunocompetent children older than 2 years and adults. Conjugation of pneumococcal polysaccharides to a carrier protein improves immune response among infants. Despite the evidence of safety and efficacy in reducing invasive pneumococcal infections, the current available vaccine is underused [91].

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