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Review

Penicillin-resistant pneumococci—implications for management of community-acquired pneumonia and meningitis

Hisham M. Ziglam[(1)] and Roger G. Finch[(2)]

Penicillin-nonsusceptible *Streptococcus pneumoniae* isolates have become increasingly prevalent worldwide. They are well-known agents of community-acquired infections such as otitis media, pneumonia and bacterial meningitis. Therapy of pneumococcal infections is made difficult by the emergence and spread of bacterial resistance to penicillin and other beta-lactams, as well as other antimicrobials such as macrolides. This article reviews current concepts of epidemiology and the implications of penicillin-nonsusceptible pneumococci for management of community-acquired pneumonia and meningitis.

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Streptococcus pneumoniae is the most common cause of pyogenic meningitis, community-acquired pneumonia, and acute otitis media. Mortality and suppurative complications associated with pneumococcal infections decreased dramatically following the introduction of penicillin therapy in the 1940s. However, pneumococcal strains with decreased susceptibility to penicillin were identified in Australia and Papua/New Guinea in the 1960s[1,2] and subsequently South Africa in the 1970s,[3] where they were associated with failures of therapy in patients with meningitis. Isolates which were intermediately resistant (minimal inhibitory concentration (MIC) 0.1–1.0 μg/mL) or resistant (MIC=2.0 μg/mL) to penicillin became increasingly prevalent worldwide during the 1980s. Multidrug resistance also appeared. The clinical impact of pneumococcal resistance varies according to the site of infection, largely reflecting the degree of antibiotic penetration to that site, and the ability of the host immune response to clear the infection. Pneumococcal resistance has led to treatment failures in patients with meningitis and acute otitis media[4]. The impact of pneumococcal resistance on the treatment of pneumonia has been more difficult to determine,[5] although there is recent evidence that increased morbidity and mortality are associated with high-level beta-lactam resistance.[6]

[(1)]Nottingham City Hospital, Nottingham, UK; [(2)]Division of Microbiology and Infectious Diseases, University of Nottingham & Nottingham City Hospital, Nottingham, UK.

Address correspondence to Professor Roger Finch, Professor of Infectious Diseases, Division of Microbiology and Infectious Diseases, University of Nottingham & Nottingham City Hospital, Nottingham, UK. E-mail: roger.finch@nottingham.ac.uk

EPIDEMIOLOGY OF PENICILLIN-RESISTANT PNEUMOCOCCI

Drug resistance among pneumococci is not a recent phenomenon. In 1943, pneumococcal isolates resistant to sulfonamides were reported. However, the first report describing a penicillin-resistant *S. pneumoniae* (PRSP) isolate (MIC=0.6 μg/mL) was from Australia in 1967, followed by an isolate with a penicillin MIC of 0.5 μg/mL isolated in New Guinea in 1969. By 1974, the prevalence of PRSP in Australia and New Guinea approached 12%. However, the first major report of the significant health impact of penicillin resistance was in 1977, from South Africa, among *S. pneumoniae*, where epidemic pneumococcal meningitis occurred with clearly resistant strains (MICs of 4–8 μg/mL). Since then, the frequency of PRSP has been increasing throughout the world.

The rate at which PRSP are emerging is alarming. There has been a 60-fold increase in the number of resistant isolates, including >20 different serotypes, during the past 5–7 years.[7] The overall incidence of PRSP in the USA has increased from <5% before 1989 to 6.6% in 1991 to 33% in 1997.[8,9] Similar trends have been observed in other countries. The overall prevalence of PRSP from Canadian laboratories was 21.2%.[10] In Spain, penicillin resistance increased sharply until 1989,[11] but it has since remained stable, with a resistance rate among invasive pneumococci of about 42%. In many countries with low resistance rates during the previous decade, there has been a remarkable increase in the 1990s, similar to that which occurred in Spain in the 1980s. In France it increased from 3.2% in 1987 to 43% in 1999. In contrast, the incidence of PRSP has remained stable at relatively low levels in other areas of Europe: Denmark, 0.1%; Germany, 1.8%; Belgium, 2–4%; Sweden, 1.7%; Finland, 1.7%; and Italy, 5.5%.[12,13] In the UK, resistance rates among isolates referred to the PHLS increased from 1.5% to 8.9% in 2000.

The pneumococcal serotypes most commonly associated with penicillin resistance are those most often responsible for infection and carriage in children, namely 6, 14, 19 and 23F.[14] The most widespread of these is often referred to in the literature as the Spanish/USA serotype 23F clone. Isolates belonging to this clone are resistant to penicillin, tetracycline, and chloramphenicol, and often to macrolides, trimethoprim and sulfamethoxazole as well. The Spanish/USA clone was identified as a major component of the penicillin-resistant pneumococcal flora in countries on five continents. Pneumococci belonging to this clone are not only geographically widespread but also represent a considerable proportion of penicillin-resistant pneumococci in a given epidemiological setting.

However, it is difficult to explain how the Spanish clones 6B and 23F have spread to and become established in regions as remote as Iceland or South Korea[15] but have not become prevalent in the UK or Germany, in spite of major tourism between these countries. Likewise, the Spanish clone 6B was detected in Iceland[15] and Finland simultaneously, yet, surprisingly, the epidemic spread of clone 6B took place in Iceland but not in Finland.

Some circulating resistant clones, such as the multidrug-resistant serotype 19F, are variants of the Spanish 23F clone which arose from horizontal transfer of capsular genes.[16] Other clones have emerged as result of horizontal spread of altered penicillin-binding protein *pbp* genes (e.g. the penicillin-resistant serotype 9V clone).[17,18] Although clonal spread, horizontal transfer and antibiotic policy seem to have a definitive influence on PRP prevalence, there are many aspects of the epidemiology that are not easily explained.

Six serotypes (i.e. 6A, 6B, 9, 14, 19F, and 23F) account for more than 80% of resistant isolates. These serotypes are all represented in the currently available pneumococcal polysaccharide vaccines. The new pneumococcal conjugate vaccine in which purified polysaccharides of the epidemiologically most important serotypes are conjugated to a carrier protein has recently been developed, and its impact on pneumococcal lower respiratory tract infections will be awaited with interest. Serotypes 1, 3, 4, 5, 7, 11, 15 and 18 rarely carry antibiotic resistance genes.

MECHANISM OF ANTIMICROBIAL RESISTANCE

Penicillin resistance is a result of gene mutations that lead to alterations in penicillin-binding proteins (PBPs). Alteration of PBPs decreases binding of penicillin and other beta-lactam antibiotics, including cephalosporins, to bacterial targets. Antibiotic resistance is a stepwise process, with successive mutations resulting in increasing resistance. Resistance is not dependent on beta-lactamases; thus, beta-lactam/beta-lactamase inhibitor combinations (e.g. amoxicillin/clavulanate) are no more effective than beta-lactam antibiotics alone. Even though mechanisms of resistance differ, rates of resistance to non-beta-lactam antimicrobials are higher in penicillin-resistant strains. Resistance to non-beta-lactam antibiotics may be acquired through several mechanisms: transformation, in which free DNA encoding alterations is acquired from other bacteria by pneumococci and incorporated into their own DNA (e.g. from the viridans group streptococci); transposons mediated; spontaneous mutations due to selection pressure. All can result in all beta-lactam antimicrobials having decreased binding affinity for PBPs. Recently, new types of modification of PBPs corresponding to resistance to broad-spectrum penicillins (e.g. PBP2b, resulting in greater resistance to piperacillin) and cephalosporins (e.g. PBP2x, resulting in greater resistance to cefotaxime) have been discovered.[19]

Risk factors for carriage or infection with resistant pneumococcal strains include prior antibiotic use,[20] age less than 5 years,[21,22] attendance at daycare centers,[23] and severe underlying disease including hematological malignancy and human immunodeficiency virus infection.[24] Resistant isolates are more commonly isolated from the middle ear and paransasal sinuses.

Recent studies have found a higher rate of recovery of antibiotic-resistant pneumococci from HIV-infected patients. Alcoholism and age >65 years are also associated with an increased risk. Some of the same risk factors in children apply to adults, particularly with regard to cohorting and recent antibiotic use. Pallares et al demonstrated that recent antibiotic use and hospitalization are important clues to a potential drug-resistant infection.[25] Interestingly, resistance is reported less commonly among invasive organisms than in those from upper airway colonization or infection. This may be explained in part by bias in sampling, as otitis and sinusitis are usually treated empirically without obtaining a culture until primary treatment has failed. Middle ear and sinus isolates are thus more likely to have been exposed to repeated courses of antibiotics. Noninvasive strains in the upper airway also have prolonged contact with the viridans streptococci thought to be the reservoir of resistance genes.

MANAGEMENT OF SERIOUS INFECTIONS

Meningitis

Following the reports of treatment failures caused by pneumococcal isolates with decreased susceptibility to penicillin in the 1970s, pneumococci with penicillin MICs between 0.1 and 1.0 mg/L became increasingly associated with microbiological and/or clinical treatment failures in patients with pneumococcal meningitis. For treatment to be successful, cerebrospinal fluid (CSF) concentrations need to be 10–100-fold higher than the MIC. Penicillin does not routinely achieve adequate

Table 1. Comparison of North American & European treatment guidelines for the initial empirical management of community acquired pneumonia

North American countries		
Infectious Diseases Society of America[36] *Outpatients* Macrolide or fluoroquinolone or Doxycycline	*Inpatients* β-lactam+macrolide	*Severe* β-lactam+macrolide β-lactam+fluoroquinolone
American Thoracic Society[37] *Outpatient* • without co-morbidity Advanced generation macrolides (e.g clarithromycin) Doxycycline • with co-morbidity β-lactam+macrolides or doxycycline Antipneumococcal fluoroquinolones	*Inpatient* • without co-morbidity IV azithromycin *Doxycycline+β-lactam* Antipneumococcal fluoroquinolone • with co-morbidity IV β-lactam+IV or oral macrolides IV antipneumococcal fluoroquinolone	*ICU patient* • No pseudomonas risk IV β-lactam+IV macrolide IV fluoroquinolone • High risk pseudomonas IV antipseudommonal β-lactam IV ciprofloxacin
Canadian Infectious Diseases Society and the Canadian Thoracic Society[38] *Outpatient/nursing home* • without comorbidity Macrolide or doxycycline • with comorbidity: COPD/ no oral steroid & no antibiotic in last 3 months Macrolides or doxycycline COPD/has steroid or antibiotics in last 3 months: Fluoroquinolone or amoxicillin/clavulanate+macrolides	*Hospitalized patients* • ward managed: Levofloxacin+clindamycin (Trovafloxacin if aspiration) *Cephalosporins+macrolide*	*ICU managed* • if Pseudomonas not suspected IV respiratory fluoroquinolones+cefotaxime IV macrolides + cefotaxime • if Pseudomonas suspected Antipseudomonal fluoroquinolones+ *antipseudomonal β-lactam or aminoglycoside* Antipseudomonal β-lactam+aminoglycoside+ either macrolides or fourth generation quinolone (levofloxacin, trovafloxacin)
European countries		
European Respiratory Society[39]: *Outpatients* Amoxicillin or tetracycline Cephalosporin or fluoroquinolone Streptogramin or macrolides	*Inpatients* β-lactams±macrolides	*Severe CAP* β-lactam+fluoroquinolone Macrolide±rifampicin
UK (British Thoracic Society)[40] *Home treated* Amoxicillin or macrolides	*Hospital treated (not severe)* oral amoxicillin+macrolides IV ampicillin+macrolides or Fluoroquinolone (levofloxacin)	*Hospital treated (severe)* Co-amoxiclav or cephalosporins macrolide Fluoroquinolone+IV benzylpenicillin
France[41] *Non-severe* Aminopenicillin or macrolide	*CAP Severe CAP* Macrolide or fluroquinolone + β-lactam	
Spain[41] *Non-severe* Penicillin or macrolides	*CAP Severe CAP* Macrolide+β-lactam	
Italy[42] *Non-severe CAP* Aminopenicillin ± macrolides	*Severe CAP* Macrolide+β-lactam	
Germany[43] *Non-severe CAP* Cephalosporin or macrolides	*Severe CAP* Macrolide+β-lactam	

levels in the CSF (CSF peak concentrations need to be about 1.0 mg/L to reliably treat meningitis caused by intermediately susceptible strains (penicillin MIC 0.1–1.0 mg/L)).

By the mid-1980s, the third-generation cephalosporins ceftriaxone and cefotaxime were widely used in the empirical treatment of suspected bacterial meningitis in childhood. *S. pneumoniae* isolates were initially uniformly susceptible to these cephalosporins. However, by the early 1990s, as penicillin-resistant pneumococcal isolates became more widespread, treatment failures associated with strains of reduced susceptibility to cefotaxime or ceftriaxone were also reported.

Vancomycin has been increasingly used in the treatment of pneumococcal meningitis resistant to penicillin and chloramphenicol, and when high-dose cephalosporins have failed.[26] CSF concentrations are increased in the presence of inflammation. The simultaneous use of dexamethasone is known to reduce CSF concentrations.[27] Vancomycin may also have a place in combination with cephalosporins when diminished susceptibility to the cephalosporin has been demonstrated.[28]

Optimal therapy for meningitis caused by PRSP is still not established. Several options are available and should be selected on the basis of the local epidemiology of resistance when this is known. Where the majority of isolates remain sensitive to penicillin, this drug can continue to be used, although for empirical therapy, ceftriaxone is a more reliable choice. Where resistance rates are high, it seems prudent to treat all patients with purulent meningitis empirically with vancomycin combined with either cefotaxime or ceftriaxone while awaiting CSF culture and antimicrobial susceptibility test results. Alternative regimens for penicillin and cephalosporin-resistant pneumococcal meningitis include: rifampicin with either ceftriaxone or cefotaxime; rifampicin and vancomycin; and vancomycin combined with chloramphenicol. Cefepime, a broad-spectrum cephalosporin, and meropenem, a carbapenem antibiotic, have both been evaluated in clinical trials for the treatment of bacterial meningitis. However, no penicillin-resistant pneumococci were included in the published studies, and the efficacy of cefepime in treating PRSP meningitis remains to be established.

In summary, the initial treatment of suspected pneumococcal meningitis should be altered, especially in areas where resistant pneumococci are regularly encountered. Initial therapy with cefotaxime or ceftriaxone combined with vancomycin is recommended. Once the results of culture and susceptibility testing are available, modifications of therapy should be made. If the strain is susceptible to penicillin, cefotaxime or ceftriaxone, vancomycin should be discontinued. Vancomycin plus cefotaxime or ceftriaxone should be used only if the organism is either intermediately or highly resistant to both penicillin and the cephalosporins. The addition of rifampicin or substitution of rifampicin for vancomycin after 24–48 h could be considered if the organism is susceptible to rifampicin or where there is evidence of an inadequate clinical or bacteriological response, or when dexamethasone has been used in the initial management. It is prudent to perform a repeat CSF examination and culture at 24–48 h, until greater experience is gained in treating meningitis caused by PRP.

Pneumonia

Pneumonia is the most serious of the lower respiratory tract infections. Community-acquired pneumonia (CAP) has an incidence of 1–3/1000, and approximately 20–42% of cases require hospitalization. One of the most important factors affecting outcome for patients with pneumonia is the prompt prescribing of appropriate antimicrobial therapy. Unfortunately, despite extensive diagnostic testing, a causative agent is identified in about 25% of routinely managed pneumonia cases, rising to about 50% in published studies, in which every effort is made to establish the diagnosis.

S. pneumoniae is the most common cause of CAP and is also responsible for a number of cases of hospital-acquired pneumonia (HAP), especially early-onset infections. Efforts should be made to establish the

Table 2. Recommended empirical regimens for treating CAP in relation to the prevalence of drug-resistant *S. pneumoniae*

	Penicillin MIC (mg/L)				
Empirical treatment	*≤0.06*	*0.12–1*	*2*	*4*	*Comments*
Outpatients					
Macrolide	+++	+	+	–	Covers atypical pathogen
Doxycycline	+++	++	+	–	Covers atypical pathogen, not suitable for children or pregnant women
Oral β-lactam	+++	++	+	–	Does not cover atypical pathogens
Fluoroquinolone	+++	+++	++	++	Not first line because of concern of resistance
Hospitalized (non-ICU) patients					
Parenteral beta-lactam+macrolides	+++	+++	++	+	Cephalosporins have superior activity against resistant pneumococci in comparison with ampicillin/sulbactam
Fluoroquinolone	+++	+++	+++	++	Not first line because of concern of resistance

microbial etiology of all patients admitted to hospital with CAP and those developing HAP. Blood and sputum cultures should ideally be collected before starting antibiotic therapy, which should not be delayed, particularly in those with severe infection. Contiguous or metastatic sites of infection such as pleural fluid, joint fluid or the central nervous system should also be cultured if involved.

To date, no large studies have been performed to evaluate the role of sputum Gram stain or culture in the management of lower respiratory tract infections due to PRSP, much less to compare their diagnostic accuracy with that of 'gold-standard' investigations (i.e. culture of blood, transthoracic needle aspiration, or pleural fluid aspiration), since the sensitivity and specificity of sputum cultures continue to be questioned. Even if *S. pneumoniae* could be reliably identified by Gram stain, antimicrobial susceptibilities are dependent on sputum culture.

The increasing incidence of PRSP has given rise to considerable concern and variations in the recommendations for initial empirical management of CAP. Several recently published evidence-based guidelines have addressed the issue of PRSP, and yet the position of beta-lactam antibiotics and notably penicillin in the management of CAP differs considerably (Table 1). Macrolides and the new respiratory fluoroquinolones feature as recommended first-line therapy for patients managed in the community in North America. In the UK, amoxicillin remains the preferred agent for community-managed or non-severe hospital-managed infection. Macrolides are an alternative but are combined with a beta-lactam for those hospitalized and who have clearly failed community management. This combination extends the spectrum of activity to include *Legionella* spp. and atypical pathogens.

For infections shown to be due to *S. pneumoniae*, it is recommended that local susceptibility patterns be considered, since penicillin-resistant pneumococci also often exhibit reduced susceptibility to macrolides. For hospitalized ward-managed patients, an extended-spectrum cephalosporin (cefotaxime or ceftriaxone) plus a macrolide, or a beta-lactam/beta-lactamase inhibitor combined with a macrolide or a fluoroquinolone, are recommended. Fluoroquinolones are also preferred alternative therapy for patients in the intensive care unit with lung damage, aspiration or beta-lactam intolerance.

In the era of increasing pneumococcal resistance, new recommendations for the management and surveillance of CAP were recently published in a consensus paper from the drug-resistant *S. pneumoniae* therapeutic working group (DRSPTWG) (Table 2).[29] The DRSPTWG recommends that pneumococcal infections should be considered susceptible if the penicillin MIC is no greater than 1 mg/L, of intermediate susceptibility if the MIC is 2 mg/L, and resistant if the MIC is 4 mg/L or greater.

There have been few prospective studies looking at the impact of penicillin resistance on the outcome of pneumococcal pneumonia. In one study of 108 children with pneumococcal infections, 78 of whom had pneumonia, the clinical success of antimicrobial therapy was similar for PRSP and PSSP infections. However, only one isolate was highly resistant to penicillin.[30] Another study of 75 patients with pneumococcal pneumonia found no increase in mortality related to decreased penicillin susceptibility, although the MICs of isolates were not reported;[31] similar results were reported from San Francisco.[32]

The macrolide antimicrobials have been used successfully to treat respiratory infections for many decades. They have a broad spectrum of activity, providing coverage against key respiratory pathogens, including atypical/intracellular pathogens. However, erythromycin resistance among pneumococci is now a major concern. Pneumococcal macrolide resistance is usually expressed as one of two phenotypes. The first, known as M phenotype (*mef*E gene), produces moderate levels of macrolide resistance (MICs <32 mg/L).[33] A second phenotype, MLS_B (*erm*AM gene), is usually associated with very high-level macrolide resistance (MICs >64 mg/L).[33] As a result of these in vitro reports, many prescribers are changing from macrolides to other agents, notably fluoroquinolones for pneumococcal infections, as well as for community-acquired respiratory tract infections. However, there is a paucity of data indicating that these resistance trends are translating into in vivo clinical failures.[34,35]

The recommendations for treating outpatients and hospitalized patients are outlined in Table 2. Suitable empirical agents for CAP include a macrolide, doxycycline for children aged 8 years or older, or an oral beta-lactam with good activity against pneumococci. Regimens for hospitalized patients with CAP should include an intravenous beta-lactam. The DRSPTWG report proposes that, in order to limit the emergence of fluoroquinolone-resistant strains of *S. pneumoniae*, these agents should only be used if other therapeutic options have failed, if the patient is allergic to other agents, or if the strain of *S. pneumoniae* is highly drug-resistant (MIC=4 mg/L).

CONCLUSION

The prevalence of drug-resistant *S. pneumoniae* is increasing but varies considerably throughout the world. The clinical significance of this resistance is poorly defined, especially in relation to the treatment of pneumococcal lung disease. There is clear evidence that PRSP causing meningitis fail to respond to conventional management, while high-level resistance to macrolides is beginning to be reported as a cause of failure in pneumococcal pneumonia. Unless there is a dramatic change in the antibiotic-prescribing habits of physicians and other health care workers, it is unlikely

that this upward trend in antibiotic resistance will continue. At present, the preferred treatment of pneumococcal pneumonia continues to be penicillin (benzylpenicillin or amoxicillin). Empirical use of other agents such as macrolides and doxycycline still has a role in the community management of nonsevere CAP. However, pneumooccal meningitis in area with an incidence of high resistance now requires a third-generation cephalosporin, either alone or in combination with vancomycin. Once the results of culture and susceptibility testing are available, treatment can be modified. For the newer agents, such as meropenem and respiratory fluroquinolone, more information on dose and duration of therapy is urgently required. The role and position of conjugate pneumococcal vaccine should be rapidly defined and could contribute significantly to the management of PRSP infection through prevention.

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