Clinical significance of antimicrobial resistance in *Streptococcus pneumoniae*

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Despite increasing resistance in the pneumococcus over the past 30 years, there are few cases of treatment failure of non-meningeal infections with high-dosage parenteral penicillin G, which still remains highly effective for many pneumococcal diseases. This is reflected by the new 2008 CLSI breakpoints for parenteral penicillin G of susceptible, ≤2 μg/ml, intermediate, 4 μg/ml, and resistant, ≥8 μg ml, for non-meningeal infections. For meningitis and oral penicillin V use, the old penicillin breakpoints of susceptible, ≤0.06 μg/ml, intermediate, 0.12 - 1 μg/ml, and resistant, ≥2 μg/ml, will remain in place. Clinically relevant susceptibility breakpoints have also been developed for virtually all relevant antimicrobial agents used to treat pneumococcal diseases, based on clinical studies and pharmacokinetic and pharmacodynamic parameters. Although pneumococcal resistance to β-lactams, macrolides and co-trimoxazole is now common worldwide, we are still able to treat almost all pneumococcal infections adequately. An exception is the oral treatment of multidrug-resistant serotype 19A strains in children in the USA, as these are resistant to amoxicillin, oral cephalosporins, macrolides, clindamycin and co-trimoxazole. While there is a need to develop new agents, judicious use of antimicrobial agents is the best long-term approach. Empiric treatment guidelines should reflect the emerging threats from increased drug resistance and the possibility of increased virulence in replacement serotypes following vaccine use. Compliance with guidelines by physicians and patients is important to prevent further development of resistance.

Streptococcus pneumoniae is a common cause of community-acquired bacterial respiratory infections, including pneumonia, meningitis, bacteraemia, otitis media, and sinusitis, and is the pathogen least likely to resolve without treatment.[1] The pneumococcus accounts for more than a third of acute bacterial sinusitis, over half of community-acquired bacterial pneumonia, and nearly a third of acute otitis media in children. In adults it is responsible for 20 - 75% of community-acquired pneumonia, 15 - 30% of acute exacerbations of chronic bronchitis, and 20 - 40% of acute sinusitis.[2] Of particular concern is the estimated annual incidence of 150 million cases of clinical pneumonia in children under 5 years of age in developing countries, with 11 - 20 million severe enough to require hospitalisation, compared with an annual incidence of 2.1 million cases in developed countries.[3] More than 4 800 deaths are estimated to have occurred from invasive pneumococcal disease in the USA in 2005.[4]

The capsular polysaccharide is the major virulence factor for pneumococcal disease and also provides the antigenic target for production of protective antibodies either naturally or by vaccine. There are at least 90 immunologically distinct capsular serotypes in 21 numbered serogroups, each containing 2 - 5 related serotypes, with a total of 65 such serotypes, and another 25 individually numbered serotypes. Sequential serotypes of pneumococci colonise the nasopharynx, beginning within a few months of birth and continuing throughout adolescence and adulthood.[5] Most serotypes colonise the nasopharynx for a month to a year, and are then replaced by another, with immunity developing to each colonising serotype sequentially, and duration and prevalence of colonisation decreasing with age. The prevalent serotypes carried differ between adults and children, with most of the serotypes carried by children under 3 years of age belonging or related to those included in the recently licensed 7-valent protein-conjugated pneumococcal vaccine (4, 6B, 9V, 14, 18C, 19F, 23F), although serotypes 1, 3, 5, and 7F are important in this age group in developing countries.[6] Person-to-person transmission of *S. pneumoniae* is direct or through fomites, and is facilitated by crowding, such as in day-care centres. Pneumococcal disease occurs when an intercurrent event, such as an acute viral infection, damages the respiratory epithelium, resulting in infections of the middle ear space, mastoid air spaces, paranasal sinuses, bronchi and lung parenchyma, or in bacteraemia with haematogenous spread to other sites such as the meninges and joint spaces.

Work on pneumococcal vaccines began in 1911 in South Africa by Sir Almroth Wright and subsequently F Spencer Lister because of the extremely high incidence and mortality of lobar pneumonia in workers in gold and diamond mines.[7] The annual incidence in one diamond mine between 1908 and 1911 was 70 - 154 per 1 000 and mortality 14 - 29 per 1 000. The efficacy of these early, killed, whole-cell vaccines was striking, with the annual incidence of lobar pneumonia in this mine reduced to <5 per 1 000 and mortality <1 per 1 000 per year by 1916 - 1917. A similar result was reported by Cecil and Austin on a killed, whole-cell vaccine used in an American army camp in 1918. In 1977, the first modern pneumococcal vaccine, a 14-valent

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purified capsular polysaccharide vaccine targeted at elderly and high-risk populations, was approved.[8,9] In 1983, it was replaced by a 23-valent polysaccharide vaccine (Pneumovax 23, Merck, Whitehouse Station, NJ) that included antigen from the 23 serotypes that cause 88% of invasive diseases in adults and cross-reactivity for types that account for an additional 8% of invasive disease.[10] The vaccine is estimated to be about 60 - 70% effective against invasive disease. As polysaccharide vaccines are ineffective in children under 2 years of age, various protein-polysaccharide conjugated vaccines have been developed, and a 7-valent vaccine (Prevnar, Wyeth-Lederle, Pearl River, NY) was introduced in the USA in 2000.[11] The vaccine contains purified polysaccharides from the 7 serotypes commonly responsible for invasive disease in children in the USA, including the 5 most often found to be highly or multiply drug resistant. Recent studies have shown it to be efficacious in preventing invasive disease as well as carriage and associated respiratory infections caused by the vaccine serotypes.[12] Less encouraging news is the emergence of replacement serotypes, particularly 19A, which are equally invasive and multiply drug resistant.[13,14]

Development of resistance

Pneumococcal disease was one of the first infectious diseases against which targeted therapy was aimed, with type-specific equine and rabbit antisera, optochin and early sulfonamides studied during the second and third decades of the 20th century.[7,9] The introduction of penicillin G in the 1940s replaced these earlier therapies, and the subsequent introduction of tetracyclines, chloramphenicol, macrolides, lincosamides, vancomycin, newer sulfonamides, trimethoprim, fluoroquinolones and linezolid provided additional therapeutic options.[1,15,16] It is noteworthy that resistance to most of these antimicrobial agents was described soon after their introduction, although reports of resistance between 1950 and 1975 were infrequent, and little penicillin resistance of clinical significance was reported. This situation changed drastically in 1977 with the isolation of serotype 19A isolates from children with bacteraemia and meningitis in Durban and Johannesburg, South Africa, that were highly resistant to penicillin G and other β-lactams as well as chloramphenicol.[17,18] These strains were resistant to ampicillin and chloramphenicol, the agents of choice for empiric treatment of meningitis at that time. Many of the Johannesburg isolates were also resistant to macrolides, lincosamides, tetracycline and trimethoprim-sulfamethoxazole.

Clinical significance of resistance

Since the largest number of prescriptions for antimicrobials is for respiratory infections in outpatients, there is considerable selective pressure on the pathogens causing these diseases. This generally occurs at the site of carriage of these bacteria (the nasopharynx) but can occasionally occur at the site of infection. In addition, the other colonising flora, such as viridans group streptococci, are exposed to these agents and often develop resistance which can in turn be transferred to *S. pneumoniae*. Resistance to antimicrobial agents in the major bacterial respiratory tract pathogens has increased alarmingly in recent years, leading to a need to re-evaluate empiric treatment choices. Drug resistance emerges more rapidly in the paediatric population than in adults, largely as a function of the higher frequency and density of bacterial colonisation of the nasopharynx in children.[5] Antimicrobials should therefore be used judiciously as a large proportion of respiratory infections are viral in origin, where no antibiotic is indicated, and many bacterial infections resolve without antimicrobial treatment.[19,20]

Our understanding of the relationships between *in vitro* and *in vivo* susceptibility of pneumococci has been limited by the lack of adequate clinical studies. These limitations have to a large extent been overcome recently with bacteriological outcome otitis media studies [21] and with the development of the field of pharmacokinetics and pharmacodynamics (PK/PD), which enables extrapolation of animal model data to humans.[22] Pharmacokinetics describes the body's absorption, distribution, metabolism, and elimination of drugs, while pharmacodynamics examines the *in vivo* relationship between the target pathogen and the antimicrobial agent over time, taking into account the effects of variations in drug concentrations on organism growth dynamics. Antimicrobials can be divided into time- and concentration-dependent agents based on PK/PD relationships. For time-dependent agents such as β-lactams, the duration of the nonprotein-bound (free or active) drug concentration in plasma over time relative to the minimum inhibitory concentration (MIC) of the agent against a pathogen will determine *in vivo* bacterial killing. For *S. pneumoniae* the free (non-protein-bound) plasma concentration of a β-lactam should be above the MIC of the agent for at least 30 - 35% of the dosing interval for penicillins, 40 - 50% for cephalosporins and 20 - 25% for carbapenems. Thus the free plasma concentrations of an agent, based on standard dosing regimens, achieved for the required proportion of the dosing interval can be determined and used as the susceptibility limit or pharmacodynamic breakpoint.[22] Most agents other than β-lactams are concentration dependent, with the ratio of non-protein-bound plasma area-under-the-curve (AUC) value over 24 hours to MICs (AUC_{24}:MIC ratio) correlated with *in vivo* efficacy. Target AUC_{24}:MIC ratios required for clinical success vary between drug classes, and are around 30 for macrolides, lincosamides and fluoroquinolones, and 80 for linezolid; susceptibility breakpoints for these agents can therefore be calculated by dividing AUC_{24} values by the applicable target. Susceptibility breakpoints for time- and concentration-dependent agents based on plasma pharmacokinetics are generally applicable to extracellular infections at body sites where extracellular fluid levels are directly related to non-protein-bound plasma levels, such as the respiratory tract and

dermis, but not to sites such as the central nervous system, where drug penetration may be limited. Application of PK/PD principles and appropriate clinical data has resulted in the development of clinically relevant breakpoints for *S. pneumoniae* infections for a variety of sites of infection and dosing regimens (Tables I and II).

Strains of *S. pneumoniae* were exquisitely susceptible to penicillin G, with MICs of ≤0.06 µg/ml when this agent was first introduced and used clinically in the 1940s and 1950s. In fact, the vast majority of strains at that time had penicillin G MICs ranging from 0.015 µg/ml to 0.03 µg/ml; this is therefore referred to as the baseline activity of penicillin G against 'wild-type' *S. pneumoniae*.[23] Decreased susceptibility to penicillin G among a few isolates of *S. pneumoniae* was noted in the 1960s in Australia and New Guinea, with MICs of 0.1 - 1 µg/ml; and in the 1970s in South Africa, isolates were noted to have penicillin G MICs as high as 2 - 4 µg/ml.[17,18] Compared with fully susceptible isolates, the most resistant of these strains were only inhibited by a more than 200-fold greater concentration and other β-lactams. Penicillin G MICs at this time were arbitrarily classified by MIC range as susceptible (MICs ≤0.06 µg/ml), intermediate (0.12 - 1 µg/ml) and resistant (≥2 µg/ml), as this had direct relevance to meningitis and to prediciting susceptibility of penicillin-susceptible isolates to other β-lactams.[18,22]

However, this classification of penicillin MICs was confusing and led to inappropriate clinical applications; therefore, 'non-susceptible' strains are best considered to be β-lactam challenged as this challenge can be overcome in many instances with appropriate dosing regimens. This situation has now largely been clarified by the Clinical and Laboratory Standards Institute (CLSI), with the development of clinically relevant susceptibility breakpoints for most β-lactams based on dosing regimen and site of infection, with breakpoints differing for meningeal and non-meningeal infections.[24] The susceptible penicillin G breakpoint remains at ≤0.06 µg/ml for meningitis and for prediction of susceptibility to other β-lactams, while new susceptibility breakpoints for non-meningeal infections have been established at ≤2 µg/ml for parenteral penicillin G dosed at 12 million units/day and ≤4 µg/ml at 18 - 24 million units/day (≤2 µg/ml, susceptible; 4 µg/ml, intermediate; ≥8 µg/ml, resistant).[24] Recent international surveillance studies have demonstrated that about 50% of strains of *S. pneumoniae* still have penicillin G MICs in the 'fully' susceptible range of ≤0.06 µg/ml, with 18 - 20% in the original intermediate range (0.12 - 1 µg/ml) and 12 - 33% in the original resistant range (≥2 µg/ml),[25-27] and these interpretations are still valid for meningitis. Application of the new penicillin G breakpoints for non-meningeal infections to one dataset results in 92.6% of isolates being susceptible (≤2 µg/ml), 7.1% intermediate (4 µg ml) and 0.3% resistant (≥8 µg/ml) (Fig. 1).[27] Although currently rare, highly penicillin G-resistant strains with MICs ≥8 µg/ml are of concern should they proliferate.[28]

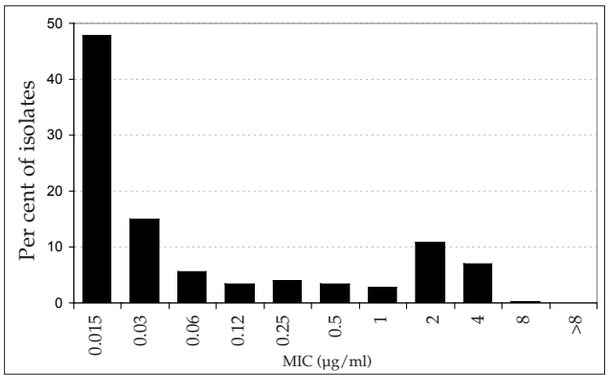

Fig. 1. Histogram of penicillin G MICs of 8 882 isolates of S. pneumoniae *from 26 countries, 1998 - 2000.*[27]

In general, the MIC distributions for all other β-lactams against *S. pneumoniae* also range over a greater than 200-fold concentration; however, there are significant differences among these agents with regard to the baseline activity,[29] and each β-lactam is best considered as an independent agent with its own breakpoints based on its pharmacokinetics and dosing regimen. Susceptibility breakpoints and susceptibility of relevant β-lactams at these breakpoints for usual dosing regimens by site of infection are shown in Tables I and II.

MIC distributions for other antimicrobial classes against which resistance has developed show distinct bimodal or trimodal patterns, with clear differentiation of 'wild-type' susceptible strains from resistant strains. Nonetheless, susceptibility breakpoints should be established based on PK/PD parameters applicable to each agent and clinical studies to determine clinically relevant breakpoints. In most cases, the susceptible breakpoint falls between the susceptible 'wild-type' and resistant populations; susceptibilities of relevant agents at these breakpoints are shown in Tables I and II.

Macrolides show a trimodal MIC distribution, representing 'wild-type' strains with low MICs (<1 µg/ml), strains with efflux-mediated resistance with MICs usually 1 - 8 µg/ml for most macrolides, and strains with ribosomal methylase-mediated resistance with MICs usually >64 µg/ml.[23] Strains with efflux-mediated resistance are susceptible to lincosamides, while those with ribosomal methylase-mediated resistance are not. Considerable effort has been expended on determining where the clinically relevant macrolide breakpoints lie. Many studies have shown that the breakpoint is between the MICs of the 'wild-type' and efflux-resistant populations in all pneumococcal diseases, including pneumonia,[15, 30-33] so this should no longer be a point of controversy, although some investigators still disagree.[34] An agent related to macrolides, the ketolide telithromycin, is available in some countries, but its advantages, if any, over macrolides have not yet been adequately investigated.[35]

Unimodal MIC distributions are found for vancomycin, linezolid, doxycycline and rifampicin, with susceptible

Table I. Susceptibility of *S. pneumoniae* to selected antimicrobials using CLSI breakpoints except for doxycycline and high-dose and extended-release amoxicillin/clavulanate, for which PK/PD breakpoints were used*

Antimicrobial agent	Susceptible breakpoint (µg/ml)	Per cent susceptibility by region							Per cent susceptibility, all isolates
		Africa	E. Europe	W. Europe	Far East	Middle East	Latin America	USA	
Parenteral agents									
Penicillin G parenteral (meningitis, high dose)	≤0.06	47.8	85.4	77.8	45.3	45.5	63.4	62.9	68.3
Penicillin G parenteral (non-meningitis, regular dose)	≤2	94.4	96.4	95.3	80.0	88.5	97.0	90.2	92.6
Penicillin G parenteral (non-meningitis, high dose)	≤4	100	100	99.8	99.0	100	99.8	99.4	99.7
Ceftriaxone (non-meningitis)	≤1	96.1	96.2	96.0	86.2	91.7	98.8	95.7	95.1
Ceftriaxone (meningitis)	≤0.5	91.1	92.0	86.6	60.5	74.5	88.6	77.8	82.6
Oral agents									
Penicillin V	≤0.06	47.8	85.4	77.8	45.3	45.5	63.4	62.9	68.3
Amoxicillin (regular dose)	≤2	96.3	98.3	97.2	93.0	95.2	96.3	90.9	95.1
Amoxicillin/clavulanate (regular dose)	≤2	97.6	98.5	97.5	93.3	95.5	96.5	91.6	95.5
Amoxicillin (high dose)	≤4	99.8	99.1	99.0	99.5	99.4	98.6	94.7	97.9
Amoxicillin/clavulanate (high dose and extended release)	≤4	99.8	99.1	99.0	99.5	99.4	98.6	94.7	97.9
Cefaclor	≤0.5	58.9	83.8	72.6	22.2	39.5	67.6	45.6	60.2
Cefuroxime axetil	≤1	88.9	91.0	84.3	54.0	71.0	80.9	70.9	78.6
Cefixime	≤1	47.8	85.4	77.8	45.3	45.5	63.4	62.9	68.3
Cefprozil	≤1	89.8	91.6	85.3	54.5	68.8	83.7	72.7	79.7
Cefdinir	≤0.5	87.2	90.8	81.8	50.6	64.4	77.3	70.0	76.5
Doxycycline	≤0.25	67.4	71.6	76.1	24.8	77.4	70.4	79.0	71.3
Co-trimoxazole	≤0.5/9.5	44.3	68.2	71.3	51.5	50.3	46.4	62.5	63.3
Oral and parenteral agents									
Erythromycin	≤0.25	90.0	93.0	77.6	32.7	82.5	84.1	71.2	75.3
Clarithromycin	≤0.25	90.0	93.2	77.6	32.9	82.8	84.6	71.6	75.5
Azithromycin	≤0.12	90.0	93.0	77.6	32.7	83.1	84.1	71.3	75.4
Clindamycin	≤0.25	91.1	95.0	81.6	68.8	93.0	90.2	90.3	86.0
Chloramphenicol	≤4	90.6	86.9	89.9	63.2	94.3	94.2	91.3	88.1
Levofloxacin	≤2	99.8	99.9	99.8	94.9	99.7	99.5	99.1	99.2
Gemifloxacin	≤0.25	100	100	100	99.6	100	99.8	99.7	99.9
Moxifloxacin	≤1	100	100	99.9	97.4	100	100	99.4	99.6

*Data adapted from the Alexander Project, 1998 - 2000,[27] with application of new penicillin G breakpoints.[24]

Table II. Adult and paediatric dosing regimens and susceptibility of antimicrobial agents used to treat pneumococcal infections.[19,20,37,40,48,49] Dosing regimens are shown as total recommended daily dose and number of doses per day, and should be used in conjunction with local prescribing information. Susceptibility data reflect overall findings from international studies and local susceptibility data should be taken into consideration as susceptibility patterns vary considerably

	Total daily dose (number of doses per day)				
Antimicrobial agent	Adults	Infants and children	Susceptible breakpoint (µg/ml)*	Per cent susceptibility	Data source
Parenteral agents – meningitis					
Penicillin G	24 million units (6)	300 000 - 400 000 U/kg (4 - 6)	≤0.06	68.3	27
Ampicillin	12 g (6)	300 mg/kg (4)	Penicillin ≤0.06	68.3	27
Ceftriaxone	4 g (1 - 2)	100 mg/kg (1 - 2)	≤0.5	82.2 - 86.2	27, 50
Cefotaxime	8 - 12 g (4 - 6)	225 - 300 mg/kg (4 - 6)	≤0.5	87.4	50
Cefepime	6 g (3)	150 mg/kg (3)	≤0.5	85.3	50
Meropenem	6 g (3)	120 mg/kg (3)	≤0.25	78.1 - 93.9	51
Vancomycin	30 - 60 mg/kg (3 - 4)	60 mg/kg (4)	≤1	100	52
Rifampicin	600 mg (1)	20 mg (1 - 2)	≤1	99.9	53
Chloramphenicol	4 - 6 g (4)	75 - 100 mg/kg (4)	≤4	88.1	27
Parenteral agents – non-meningeal infections					
Penicillin G (regular dose)	12 million units (6)	250 000 - 400 000 U/kg (4 - 6)	≤2†	92.6	27
Penicillin G (high dose)	18 - 24 million units (6)	400 000 U/kg (4 - 6)	≤4	99.7§	27
Ampicillin	4 - 8 g (4)	50 - 100 mg/kg (4)	Penicillin ≤2	92.6	27
Ceftriaxone	1 - 2 g (1)	50 - 75 mg/kg (1 - 2)	≤1	95.2	50
Cefotaxime	3 g (3)	75 - 100 mg/kg (3 - 4)	≤1	95.1 - 96.5	27, 50
Cefuroxime sodium	2.25 g (3)	50 - 100 mg/kg (3 - 4)	≤0.5	75.3	50
Cefepime	2 g (2)	100 mg/kg (2)	≤1	96.5	50
Meropenem	1.5 - 3 g (3)	60 - 120 mg/kg (3)	≤0.25	78.1 - 93.9	51
Imipenem	1 - 2 g (3 - 4)	60 mg/kg (4)	≤0.12	92.4 - 96.3	51
Ertapenem	1 g (1)	30 mg/kg (2)	≤1	93.2 - 93.3	26, 54
Vancomycin	2 g (2 - 4)	40 - 45 mg/kg (3 - 4)	≤1	100	52
Oral agents					
Penicillin V	1 - 2 g (3 - 4)	25 - 50 mg/kg (3 - 4)	≤0.06†	68.3	27
Amoxicillin (regular dose)	1.5 g (2 - 3)	45 mg/kg (2 - 3)	≤2	95.1	27
Amoxicillin/clavulanate (regular dose)	1.5 g/250 mg (2 - 3)	45/6.4 mg/kg (2 - 3)	≤2	95.5	27
Amoxicillin (high dose)	6 (3)	90 mg/kg (2 - 3)	≤4	97.9	27
Amoxicillin/clavulanate (high dose and extended release)	4 g/250 mg extended release (2)	90/6.4 mg/kg (2-3)	≤4	97.9	27
Cefaclor	750 - 1 500 mg (3)	20 - 40 mg/kg (3)	≤0.5	60.2	27
Cefuroxime axetil	500 - 1 000 mg (2)	20 - 30 mg/kg (2)	≤1	78.6	27
Cefixime	400 mg (1 - 2)	8 mg/kg (1 - 2)	≤1	68.3	27
Cefprozil	500 - 1 000 mg (2)	15-30 mg/kg (2)	≤1	79.7	27
Cefdinir	600 mg (1 - 2)	14 mg/kg (1 - 2)	≤0.5	76.5	27
Doxycycline	200 mg day 1, then 100 mg (1)	NR‡	≤0.25	71.3	27
Co-trimoxazole	320/1 600 mg (2)	8/40 mg/kg (2)	≤0.5/9.5	63.3	27
Oral and parenteral agents					
Levofloxacin	500 - 750 (1)	NR‡	≤2	99.2	27
Gemifloxacin	320 (1)	NR‡	≤0.25	99.9	27
Moxifloxacin	400 (1)	NR‡	≤1	99.6	27
Erythromycin	1 - 2 g (4)	30 - 50 mg/kg (4)	≤0.25	75.3	27
Clarithromycin	500 - 750 mg (1 - 2)	15 mg/kg (2)	≤0.25	75.5	27
Azithromycin	500 mg day 1, then 250 - 500 mg (1)	10 mg/kg day 1, then 5 - 10 mg/kg (1)	≤0.12	75.4	27
Clindamycin	600 - 1 200 mg (4)	8 - 16 mg/kg (4)	≤0.25	86	27
Linezolid	1 200 mg (2)	30 mg/kg (3)	≤2	100	50

*Susceptibility breakpoint for agent shown unless specified otherwise.
†Non-meningeal isolates susceptible to penicillin G at this breakpoint can be considered susceptible to parenteral ampicillin, cefepime, cefotaxime and ceftriaxone. Non-meningeal isolates susceptible to ≤0.06 µg/ml of penicillin G can also be considered susceptible to these parenteral agents, as well as to parenteral ertapenem, imipenem and meropenem and to oral ampicillin, amoxicillin, amoxicillin/clavulanate, cefaclor, cefdinir, cefditoren, cefprozil, cefuroxime and cefpodoxime.
‡NR = not recommended for use in infants and children.
§Includes penicillin G susceptible (92.6%) and intermediate (7.1%) isolates based on new, non-meningeal, parenteral penicillin G susceptibility breakpoints.[24]

breakpoints above the MIC distributions of these agents with the exception of doxycycline, where the breakpoint falls within the MIC distribution. Fluoroquinolones with antipneumococcal activity (e.g. levofloxacin, moxifloxacin and gemifloxacin) are highly active against the majority of strains of *S. pneumoniae*; however, resistance has been found in many areas and is clinically significant.[36]

Treatment of *S. pneumoniae* infections

Empiric treatment of diseases associated with *S. pneumoniae* infections should take into account the spectrum of common pathogens, the probability of pneumococcal involvement, and the degree of drug resistance commonly found in the patient's geographical area.

Community-acquired pneumonia

The 2007 US treatment guidelines for empiric outpatient treatment of pneumonia in previously healthy adult patients without known risks for drug-resistant *S. pneumoniae* include a macrolide, such as azithromycin, clarithromycin, or erythromycin, or doxycycline.[37] In outpatients with comorbidities or immunosuppressing conditions, or use of antimicrobials within the previous 3 months, or in regions with >25% macrolide resistance, and for non-ICU inpatients, the guidelines suggest using a macrolide in combination with a β-lactam, such as high-dose amoxicillin or amoxicillin clavulanate, preferentially, or cefpodoxime, cefuroxime or intramuscular (IM) ceftriaxone. Doxycycline may be used as an alternative to the macrolide. A respiratory fluoroquinolone, such as levofloxacin, moxifloxacin, or gemifloxacin, is also recommended as an alternative to a macrolide in combination with a β-lactam, particularly for β-lactam allergic patients. Guidelines in other regions generally recommend β-lactams such as amoxicillin rather than macrolides as first-line agents.[38] High-dose amoxicillin, either alone or with the addition of clavulanate, is recommended for first-line outpatient treatment of children with moderate disease severity.[39] If oral antibiotics are not tolerated, daily IM ceftriaxone is recommended. Parenteral β-lactam agents, including penicillin G, cefotaxime and ceftriaxone, are recommended for hospitalised children, provided that appropriate doses of these agents are used.

Meningitis

Initial empiric treatment of meningitis for patients older than 1 month is vancomycin plus a third-generation cephalosporin such as ceftriaxone or cefotaxime.[40] In patients over 50 years of age, ampicillin should be added to cover *Listeria monocytogenes*. Treatment can be adjusted once culture and susceptibility results are obtained. For fully penicillin G-susceptible strains (penicillin G MICs ≤0.06 μg/ml), vancomycin can be discontinued, and treatment with cefotaxime or ceftriaxone continued, or high-dose penicillin G substituted. For strains with penicillin G MICs ≥0.1 μg/ml but susceptible to cefotaxime or ceftriaxone at their meningitis breakpoints (≤0.5 μg/ml), vancomycin may also be discontinued. For isolates not susceptible to cefotaxime or ceftriaxone, one should continue treatment with the cephalosporin plus vancomycin, and monitor bacteriological outcome by repeat lumbar puncture; rifampicin may be added, and moxifloxacin can be considered as an alternative.[40]

Acute otitis media (AOM)

Practice guidelines published by the American Academy of Pediatrics and the American Academy of Family Physicians Subcommittee on Management of Acute Otitis Media recommend initial treatment with either amoxicillin 80 - 90 mg/kg/day or, in the case of high temperature (>39°C) or severe otalgia, amoxicillin/clavulanate 90/6.4 mg/kg/day.[19]

Sinusitis

Fewer than 2% of cases of acute viral rhinitis are complicated by acute bacterial sinusitis. Consequently, most cases of sinusitis can be treated conservatively with fluids and decongestants. Symptoms lasting more than a week or increasing in severity can be indicative of bacterial superinfection, with *S. pneumoniae* the most common bacterial pathogen. Treatment guidelines suggest treating paediatric patients with mild disease and no antibiotic exposure in the previous 4 - 6 weeks, with high-dose amoxicillin-clavulanate, high-dose amoxicillin, cefpodoxime proxetil, cefuroxime axetil, or cefdinir.[20] Patients with β-lactam hypersensitivity can be treated with trimethoprim/sulfamethoxazole, azithromycin, clarithromycin, or erythromycin. Patients with more severe disease or recent antimicrobial use should be treated with high-dose amoxicillin-clavulanate, cefdinir, cefpodoxime or cefuroxime axetil. Beta-lactam-allergic patients should be treated as described above. Guidelines for adult patients are similar to those for paediatric patients, with the addition of respiratory fluoroquinolones such as levofloxacin or moxifloxacin, for treatment of more severe disease or treatment failure.[20]

Acute exacerbations of chronic bronchitis (AECB)

About 50% of acute episodes are estimated to be caused by bacteria, predominantly *Haemophilus influenzae*, with *S. pneumoniae* the next most frequent pathogen.[41] More seriously ill patients, such as those with comorbidities or decreased respiratory function, or patients aged >65, are best treated with either high-dose amoxicillin-clavulanate or a respiratory fluoroquinolone.[42]

Conclusions

Despite years of increasing *in vitro* penicillin G resistance in the pneumococcus, there are few cases of treatment failure of non-meningeal infections with high-dose parenteral penicillin

G.[43-46] The new CLSI breakpoints for parenteral penicillin G of susceptible (≤2 μg/ml), intermediate (4 μg/ml), and resistant (≥8 μg/ml) reflected in the 2008 guidelines will greatly facilitate appropriate reporting and use of penicillin G. For meningitis and oral use, the old breakpoints of susceptible (≤0.06 μg/ml), intermediate (0.12 - 1 μg/ml), and resistant (≥2 μg/ml) remain in place for penicillin G and penicillin V. Susceptibility breakpoints have now been developed for virtually all relevant antimicrobial agents used to treat pneumococcal diseases, and application of PK/PD parameters has been of great assistance in the development of these breakpoints. Although pneumococcal resistance to β-lactams, macrolides and co-trimoxazole is now common worldwide, we are still able to treat almost all pneumococcal infections adequately. One exception is oral treatment of children with infections caused by resistant serotype 19A strains – the same resistant serotype found in South Africa in 1977, although of different clonal origin.[47] Resistant serotype 19A strains are now common in the USA following introduction of a conjugate vaccine for use in children that contains serotype 19F but not 19A polysaccharide; these strains are resistant to oral β-lactams including amoxicillin, as well as to macrolides, lincosamides and co-trimoxazole. While there is a need to develop new agents, judicious use of antimicrobial agents is the best long-term approach. Empiric treatment guidelines should continue to evolve to reflect the emerging threats from increased drug resistance and the possibility of increased virulence in replacement serotypes. It has been encouraging to note the increased use of watchful waiting in initial treatment guidelines. Compliance with guidelines by physicians and patients is important to prevent further development of resistance.

I am honoured to participate in this tribute to Hendrik Koornhof, my teacher, mentor, collaborator and colleague. This review is also dedicated to the memory of Robert Austrian, whose passion for the pneumococcus stimulated my interest in this organism, and whose recent passing marked the end of an era. I would also like to acknowledge the numerous individuals with whom I have collaborated on pneumococcal projects throughout the world; lack of space and memory lapses preclude me from naming you all. It is particularly gratifying for me that the initial investigation of the multiply resistant pneumococcal outbreak in which I participated in 1977 - 1978 has stood the test of time, and that the susceptibility methods and interpretations developed have been validated and have formed the basis of testing and interpretation currently in use worldwide.

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