REVIEW ARTICLE

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Multidrug-Resistant *Streptococcus pneumoniae* Infections

Current and Future Therapeutic Options

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Abstract

Antibacterial resistance in *Streptococcus pneumoniae* is increasing worldwide, affecting principally β-lactams and macrolides (prevalence ranging between ≈1% and 90% depending on the geographical area). Fluoroquinolone resistance has also started to emerge in countries with high level of antibacterial resistance and consumption. Of more concern, 40% of pneumococci display multi-drug resistant phenotypes, again with highly variable prevalence among countries.

Infections caused by resistant pneumococci can still be treated using first-line antibacterials (β-lactams), provided the dosage is optimised to cover less susceptible strains. Macrolides can no longer be used as monotherapy, but are combined with β-lactams to cover intracellular bacteria. Ketolides could be an alternative, but toxicity issues have recently restricted the use of telithromycin in the US. The so-called respiratory fluoroquinolones offer the advantages of easy administration and a spectrum covering extracellular and intracellular pathogens. However, their broad spectrum raises questions regarding the global risk of resistance selection and their safety profile is far from optimal for wide use in the community. For multi-drug resistant pneumococci, ketolides and fluoroquinolones could be con-

sidered. A large number of drugs with activity against these multi-drug resistant strains (cephalosporins, carbapenems, glycopeptides, lipopeptides, ketolides, lincosamides, oxazolidinones, glycylcyclines, quinolones, deformylase inhibitors) are currently in development. Most of them are only new derivatives in existing classes, with improved intrinsic activity or lower susceptibility to resistance mechanisms. Except for the new fluoroquinolones, these agents are also primarily targeted towards methicillin-resistant *Staphylococcus aureus* infections; therefore, demonstration of their clinical efficacy in the management of pneumococcal infections is still awaited.

Streptococcus pneumoniae is a major cause of morbidity and mortality in humans, associated with respiratory tract infections (community-acquired pneumonia [CAP]), bacteraemia and meningitis.[1,2] The treatment of these infections remains challenging because of the worldwide increase in antibacterial resistance,[3] and of the emergence of multidrug-resistant (MDR) phenotypes.[4]

Beginning with current epidemiological data on resistance, this review analyses the current therapeutic options for MDR pneumococci, and also briefly presents the molecules in development with improved activity against these bacteria.

1. Antibacterial Resistance in *Streptococcus pneumoniae*

1.1 Main Mechanisms of Resistance

Table I illustrates the most important mechanisms of resistance described so far in *S. pneumoniae*. β-Lactam resistance is mediated by stepwise alterations of penicillin-binding proteins (PBPs), resulting in decreased affinity of PBP1a, PBP2x and PBP2b. In resistant isolates, PBPs are encoded by mosaic genes that contain sequence blocks highly divergent from those of sensitive strains. They have been recognised as the product of transformation events, resulting from horizontal gene transfer not only among pneumococcal clones, but also among pneumococci and commensal viridans group streptococci.[5] Macrolide resistance is usually caused by the presence of the *erm(B)* or the *mefE*, renamed *mef(A)*, resistance determinants. The *erm(B)* protein encodes a 23S ribosomal RNA methylase and most pneumococcal strains that harbour this gene are resistant to 14-, 15- and 16-membered-ring macrolides, lincosamides and streptogramin B (MLS_B phenotype). The *mef(A)* protein encodes an efflux pump that leads to resistance to 14- and 15-membered-ring macrolides only.[6,7] Other mechanisms of target modifications have been described in a few clinical pneumococcal isolates.[8-11] Resistance to quinolones is usually due to mutations in topoisomerases (mainly in the parC or gyrA subunits).[12] While single mutations already reduce the activity of weak molecules (ciprofloxacin, and to some extent, levofloxacin[13]), multiple mutations in both targets are required to cause minimum inhibitory concentration (MIC) elevation for more potent molecules (moxifloxacin, gemifloxacin, garenoxacin).[14] In addition, efflux mechanisms also affect the activity of ciprofloxacin and, to a lesser extent, levofloxacin.[15,16]

1.2 Epidemiology of Resistance

Large-scale surveillance programmes have been designed in the last few decades to look for trends in antimicrobial resistance in *S. pneumoniae*. These programmes remain essential in the setting-up of evidence-based treatment guidelines. Table II summarises the current epidemiology of resistance to β-lactams, macrolides and fluoroquinolones worldwide. Breakpoint values for susceptibility or resistance are based on Clinical and Laboratory Standards Institute guidelines.[21] Of note is that penicillin breakpoints have been recently raised for non-meningitis isolates to ≤2 mg/L (susceptible; S), 4 mg/L (intermediate; I) and ≥8 mg/L (resistant; R). This change will cause an artificial but drastic decrease in the percentage of so-called 'resistant' isolates and will classify as non-resistant strains with mutated PBPs. This highlights the risk of using S-I-R classification of strains rather than considering

Table I. Main mechanisms of antimicrobial resistance in *Streptococcus pneumoniae*

Antimicrobial class	Drugs affected	Genetic support	Mechanism of resistance	References
β-Lactams	All to a variable extent	Mosaic genes	Decreased affinity of PBP1a, PBP2x and PBP2b	17
MLS_B; ketolides	All; multiple mutations needed to confer resistance to ketolides	*erm(B)*	Methylation of 23S rRNA	18
Macrolides	14- and 15-membered-ring	*mef(A)*	Active efflux	6,7
MLS_B	All	Point mutations	Mutation in the domain V of 23S rRNA critical for macrolide binding	8-11
MLS_B; ketolides	All; multiple mutations needed to confer resistance to ketolides	Point mutations	Mutation in ribosomal proteins L4 and L22	8,10,11
Macrolides, lincosamides	14- and 15-membered-ring, inducibly resistant to lincosamides	*erm(A)*	Methylation of 23S rRNA	19
Fluoroquinolones	All to variable extent	Point mutations	Mutation in parC or/and gyrA	12
Fluoroquinolones	Norfloxacin, ciprofloxacin, levofloxacin	*pmrA, patA/patB*	Active efflux	15,16
Tetracyclines	All; glycylcyclines not affected	*tet(A), tet(O)*	Ribosomal protection	18
Oxazolidinones	Linezolid[a]	Point mutations	Mutation in domain V of 23S RNA	20
Trimethoprim		Point mutations	Mutation in the dihydrofolate reductase gene	18
Sulfonamides	All	Repetition of amino acids	Dihydropteroate synthase	18
Chloramphenicol		*cat*	Chloramphenicol acetyltransferase	18

a In pneumococci, resistance to linezolid has only been described *in vitro* so far. Other oxazolidinones have not yet been evaluated in this respect.

MLS_B = macrolides, linosamides and streptogramin B; **PBP** = penicillin binding protein; **rRNA** = ribosomal RNA.

Table II. Worldwide prevalence of resistance to penicillin, macrolides and levofloxacin in *Streptococcus pneumoniae*

Country	Study design				Resistance (%)			Reference
	study period	no. of isolates	age groups	specimen diagnosis	penicillin (I/R)[a]	macrolide[b]	levofloxacin[c]	
Africa								
Kenya	1998–9	277	Adults	CAP	I+R: 43.3			24
Mozambique	2002–3	127	<15y	IPD	I: 14 R: 0	1		25
	2002–3	248	<15y	NPC	I: 52 R: 0	2		25
South Africa	2000–1	729	Children and adults	RTI	I: 30 R: 46	62	0	26
	2003	598	ND	CA-RTI	I: 22 R: 50.1	52.2		27
Latin America								
Argentina	1999–2000	55	ND	CA-RTI	I: 10.9 R: 16.4	10.9	0	28
	1999–2000	55	ND	CAP			3	29
	2000–2	134	Adults	CAP		15.6		30
	1999–2003	291	ND	CA-RTI	I: 10.9→6.3 R: 16.4→13.4	10.9→18.1		27
Brazil	1996–2000	420	Children and adults	IPD, n-IPD, LRTI	I: 18.1 R: 1.7 I+R : 20→19.5	3.1→5.2		31
	1999–2000	260	ND	CA-RTI	I: 25.8 R: 8.1	6.9	1	28
	1999–2000	260	ND	CAP			0	29
	1999–2003	989	ND	CA-RTI	I: 25.8→20.3 R: 8.1→10.1	5.8→4.7		27
Mexico	1999–2000	203	ND	CA-RTI	I: 32.5 R: 24.1	27.6	1.5	28
	1999–2000	203	ND	CAP			1	29
	1999–2003	557	ND	CA-RTI	I: 32.5→21.3 R: 24.1→23.8	26.6→27.5		27
Peru	1997–2003	272	<2y	NPC	I: 10 R: 12.7 I+R: 5.3→20			32
	2003	74	ND	CA-RTI	I: 5.3 R: 28.9	15.8		27
North America								

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Table II. Contd

Country	Study design				Resistance (%)			Reference
	study period	no. of isolates	age groups	specimen diagnosis	penicillin (I/R)[a]	macrolide[b]	levofloxacin[c]	
Canada	1997–2002	6 991	Children and adults	RTI	I: 14.6 R: 5.6	9.9	0.5→1.1	33
	1999–2003	2 132	ND	CA-RTI	I: 10.6 8.8 R: 10.6→8.3	15.7→14.7		27
	2002	2 539	Children and adults	all sites	I: 8.5 R: 6.5	14	2.7[c]	34
USA	1999–2000	337	ND	CAP			3	29
	2000–3	31 001	Children and adults	CA-RTI	I: 12.5→15.3 R: 26.3→20.2	29.4 (31–29.2)	0.9	35
	1999–2003	1 145	ND	CA-RTI	I: 10.4→18.7 R: 32.6→28.7	30.6→35.4		27
	2002–3	1 817	ND	RTI, CSF, blood	I: 15.7 R: 18.5	29.5		36
	2003–4	1 479	ND	RTI	I: 18.7 R: 13.7	25.4	1.3	37
Asia–Far East								
China	1999–2000	70	ND	CAP			14.3	29
	1995–2001	265	Children and adults	IPD	48 in <13y 30.9 in adults	63	3.8	38
	1999–2003	260	ND	CA-RTI	I: 9.5→17.1 R: 0→4.9	50.8→68.3		27
Hong Kong	1999–2003	291	ND	CA-RTI	I: 1.4→8.6 R: 57.1→64.3	70→82.9		27
Japan	1994–2002	1 860	ND				I: 6.3→0.5 R: 2.8→2	39
	1999–2002	1 752	ND	RTI	I : 19.8→28 R: 44.5→35.9	77.9→79.9	1.2	40
	1999–2003	2 526	ND	CA-RTI	I: 19.8→26.9 R: 44.5→35	77.6→79.3		27
	2001–3	114	Adults	CAP	I: 57.9 R: 22.8	75.4		41
	2002–4	392	Children	CAP	I: 39.3 R: 52.3	79.1		42
Asian Russia	2001–2	912	<5y	NPC	I: 9 R: 0.6	3.7	0	43
Taiwan	2003	137	ND	CA-RTI	I: 8.8 R: 65.7	91.2		27

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Table II. Contd

Country	Study design				Resistance (%)			Reference
	study period	no. of isolates	age groups	specimen diagnosis	penicillin (I/R)[a]	macrolide[b]	levofloxacin[c]	
	1999–2004	286	≤14y	IPD	I: 50.7 R: 25.5	93	0.3	44
Asia–Middle East								
Israel	1998–9	437	<13y	Blood and CSF	I: 22 R: 13	10		45
	2003	68	ND	CA-RTI	I: 10.3 R: 26.5	22.1		27
Saudi Arabia	2000	154	Children and adults	'Clinically significant'	I: 44.2 R:14.9	15.6	1.3	46
	2003	76	ND	CA-RTI	I: 32.5 R: 35.5	23.7		27
Europe								
Austria	1999–2000	57	ND	CAP			0	29
	1996–2002	3 012	ND	ND	I: 2.9 R: 2.2	3.2		47
	2001–3	77	≤5y	IPD	I: 21.4 R: 0	33.9		48
	2001–3	160	Adults	'Clinically significant'	I+R: 4.4	10	0	49
Belgium	1999–2000	637	ND	IPD		36.6		50
	2001–3	148	Adults	'Clinically significant'	I+R: 11.5	23.7	0.7	49
	2003–4	815	Children and adults	N-IPD	I: 15→14.7 R: 8.4→6.4	25.3→24.5	I: 3.3→2.8 R: 1.5→0.2	51
Estonia	2000–3	49	Adults	LRTI	0	2.0		52
Finland	1999–2000	910	ND	IPD	I: 4.0 R: 1.5	6.9		53
	1997–2002	31 609	ND	ND	6.8→8.5	5.5→15		54
	2002	1 007	ND	IPD (129)/n-IPD (878)		21.5		55
France	2000–2	35	≤16y	IPD	I: 31.5 R: 14.3	48.6	0	56
	2000–2	222	Adults	IPD	I: 31.5 R: 16	56.8	0.4	56
	2001–3	443	Adults	'Clinically significant'	I+R: 47.6	46.1	0.9	49
Germany	1998–9	961	Children and adults	LRTI	I+R: 6.6	10.6	0.1	57
	1999–2000	325	ND	CAP			0.3	29
	2001–3	630	adults	'Clinically significant'	I+R: 6	10.6	0.4	49

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Table II. Contd

Country	Study design				Resistance (%)			Reference
	study period	no. of isolates	age groups	specimen diagnosis	penicillin (I/R)[a]	macrolide[b]	levofloxacin[c]	
	1997–2004	1 643	children	IPD	I: 5.1 R: 1 I+R: 0.7→11.3	9.2→27.9		58
Greece	1999–2000	145	ND	'Clinical isolates'		42.8		59
Hungary	1999–2000	54	ND	CAP			0	29
	2000–2	304	ND	IPD/n-IPD	I: 37 R: 2	41.7	0	60
Italy (North-East)	Since 1997	ND	ND	ND	I+R: 35	18		61
Italy	1999–2000	114	ND	CAP			0	29
	2001–2	ND	ND	Blood	I+R: 10.8	37.6		62
	2000–2	1 623	ND	ND	I+R: 15.2→16.1	37.9→43.7	0.2	63
	2001–3	462	Adults	'Clinically significant'	I+R: 13	35.5	1.3	49
	2001–4	551	ND	CAP			5.6	64
Norway	1993–2002	2 200	ND	IPD/n-IPD		33 (IPD) 27 (n-IPD)		65
Poland	1999–2000	68	ND	CAP			0	29
	1998–2002	887	Children and adults	IPD/n-IPD	I+R: 8.7→20.3	ND		66
	1999–2003	351	ND	CA-RTI	I: 13.2→6.9 R: 13.2→23.1	23.5→29.2		27
Portugal	1999–2000	108	ND	CAP			0	29
	1999–2001	1 210	76% adults 24% ≤18y	IPD/n-IPD	I: 15.5 R: 9	13.1		67
	2001–3	174	adults	'Clinically significant'	I+R: 19	10.3	1.2	49
	1994–2004	1 331	children and adults	IPD	I+R: 12→23.2	3.7→9.1	0.3	68
European Russia	2001–2	1 144	<5y	NPC	I: 13.7 R: 0.2	4.9	0	43
Slovenia	1999–2004	ND	ND	IPD/n-IPD		4.6→11.1(IPD) 12.8→20.2 (n-IPD)		69
Spain	1999–2000	133	ND	CAP			0	29
	1999–2002	125	mean age: 59.6y	CAP	I+R: 34	33		70
	2001–2	2 721	ND	CAP	I: 23.9 R: 20.0	35.2		71

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Table II. Contd

Country	Study design				Resistance (%)			Reference
	study period	no. of isolates	age groups	specimen diagnosis	penicillin (I/R)[a]	macrolide[b]	levofloxacin[c]	
	2001–3	310	adults	'Clinically significant'	I+R: 61.9	43.6	1	49
Switzerland	1999–2003	284	ND	CA-RTI	I: 8.1→2.9 R: 4.5→8.7	9→13		27
	2001–3	52	Adults	'Clinically significant'	I+R: 17.3	17.3	0	49
The Netherlands	1999–2000	51	ND	CAP			0	29
	2001–2	797	ND	IPD/n-IPD	I: 3.4 R: 0.9	7.4		72
	ND	264	ND	ND	I: 40.0 R: 7.6	15.9		73
	1994–2002	669	ND	'Clinical isolates'		13.6		74
	1999–2000	77	ND	CAP			0	29
Turkey	1999–2003	357	ND	CA-RTI	I: 20.7→17.4 R: 14.9→19.4	14.9→18.4		27
	2002–3	238	Children	NPC	I: 17.9 R: 7	13.7		75
UK	1999–2000	91	ND	CAP			0	29
	ND	831	Children	'Clinical isolates'	I: 3.7 R: 3.7	8.8		76
Oceania								
Australia	1999–2000	114	ND	CAP			0	29
	2002	183	ND		I: 14 R: 38	53		77

a MIC 0.12–1 mg/L for intermediate strains and ≥2 mg/L for resistant strains, according to the CLSI guidelines, which were valid until mid-2007.

b Intermediate and resistant strains were counted together; erythromycin MIC = 0.5 mg/L for intermediate strains and ≥1 mg/L for resistant strains, according to CLSI guidelines.

c Intermediate and resistant strains were counted together; levofloxacin MIC = 4 mg/L for intermediate strains and ≥8 mg/L for resistant strains, according to the CLSI guidelines.

CAP = community-acquired pneumonia; **CA-RTI** = community-acquired respiratory tract infection; **CLSI** = Clinical and Laboratory Standards Institute; **CSF** = cerebro-spinal fluid; **I** = intermediate level of resistance (MIC = 0.12–1 mg/L), according to the CLSI guidelines; **IPD** = invasive pneumococcal disease; **LRTI** = lower respiratory tract infections; **MIC** = minimum inhibitory concentration; **ND** = no data; **n-IPD** = non-invasive pneumococcal disease; **NPC** = nasopharyngeal carriage; **R** = high level of resistance (MIC ≥2 mg/L), according to the CLSI guidelines; **RTI** = respiratory tract infections; → indicates figures separated by an arrow show evolution over the study period.

actual MIC values. The European Committee on Antimicrobial Susceptibility Testing (EUCAST)[22] breakpoints have not yet been published but the European agency will definitely propose lower values.

A low prevalence of penicillin resistance is observed in countries of Northern, Central and Western Europe, such as Germany and Austria. In contrast, high rates are observed in France, Spain, the US, Mexico, Africa and Asia, whereas moderate levels of resistance are reported from Belgium, Portugal, Switzerland, Italy, Canada, and most countries from Latin America. Macrolide resistance is almost parallel to that of β-lactams. Fluoroquinolone resistance begins to emerge in countries characterised by an important consumption of these drugs, together with high-resistance rates to other classes of antimicrobials, as is the case in the US, Mexico, Canada, France, Italy and Asian countries. However, the still low prevalence of fluoroquinolone resistance may be misleading since it probably hides a large reservoir of strains that have already acquired a first mutation, mostly in the DNA-gyrase system (surveillance studies generally use levofloxacin as an indicator of fluoroquinolone resistance, but first-step mutants would be more easily detected with ciprofloxacin[23]).

This inter-country variability has been documented in numerous surveillance studies, such as the Pneumoworld study,[49] the PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) study 1999–2000,[78] the Alexander Project[79,80] and the SENTRY Antimicrobial Surveillance Program.[81,82] Also of interest is the trend to a decreased prevalence of resistance, mainly to β-lactams, in some parts of the world, such as the US and some European countries.

Of more concern, a number of studies have reported an increase over the last few years in the prevalence of MDR pneumococci in the US[37,83,84] and in other parts of the world, particularly Asia,[85-88] (the first mention of such strains apparently resistant to penicillin and other antibacterials appeared in the Time magazine in 1977[89]). The frequency of isolates that were resistant to two or more classes of antibacterials in 2002 has been analysed globally and for each country participating in the PROTEKT study (table III). Globally, more than one-third of the *S. pneumoniae* isolates were MDR. The highest prevalence of multidrug resistance was among the Far Eastern countries, followed by South Africa, France, Hungary, Spain and Mexico. The Netherlands, Russia, Sweden and the UK all had low rates of multidrug resistance (<15%). Isolates that were resistant to three classes of antibacterials were the most prevalent globally (≥10%). Yet, the US had a high prevalence of isolates resistant to four classes of antibacterials. Isolates resistant to seven classes of antibacterials were present in low numbers in France, Spain and South Korea, but at worryingly high levels in Hong Kong.[90]

Multidrug resistance is often spread through resistant genetic clones and a small number of clones dominate the antimicrobial-resistant pneumococcal population.[91] The most notable was first identified in Spain in the early 1980s (Spain^{23F} clone). This clone has spread globally and has been identified in the US, Mexico, South America, other European countries, South Africa and Asia. As a result of the evolution of international clones, an understanding of resistance patterns is essential to the successful control of these bacteria. Multilocus sequence typing is increasingly being used to identify the predominant clones.[92,93] This method is highly portable, because any laboratory can compare the sequences of the seven loci in their isolates with those in a central database on the World Wide Web (http://www.mlst.net) and obtain the allelic profile of each isolate. Standardisation of the typing of strains using this technique, as well as pulsed-field gel electrophoresis and PBP fingerprinting, allowed the establishment in 1997 of the Pneumococcal Molecular Epidemiology Network, with the aim of global surveillance of antibiotic-resistant strains and of standardisation of nomenclature and classification of resistant clones.[1] Another strategy to avoid the spreading of MDR clones, while at the same time reducing the burden of pneumococcal disease, is

1 The website of this network (http://www.sph.emory.edu/PMEN/index.html) presents the criteria for inclusion of clones in the database and depicts the main characteristics of the 43 epidemic clones described so far.

Table III. Frequency of multidrug resistance[a] among isolates of *Streptococcus pneumoniae* by country in 2002 (reproduced from Reinert,[90] with permission)

Country	No. of isolates	% of total isolates						
		2-MDR	3-MDR	4-MDR	5-MDR	6-MDR	7-MDR	total MDR
Latin America								
Argentina	80	7.5	8.8	1.3	3.8	0.0	0.0	21.3
Brazil	238	5.9	12.6	3.4	0.8	1.3	0.0	23.9
Ecuador	50	6.0	18.0	8.0	4.0	4.0	0.0	40.0
Mexico	194	13.4	29.4	10.3	3.1	6.2	0.0	62.4
Peru	74	4.1	18.9	13.5	8.1	1.4	0.0	45.9
North America								
Canada	628	2.7	7.2	1.4	3.0	1.9	0.0	16.2
USA	292	3.4	6.8	13.4	4.5	6.5	0.0	34.6
Asia								
China	74	5.4	13.5	56.8	5.4	16.2	0.0	97.3
Hong Kong	74	1.4	10.8	8.1	32.4	18.9	5.4	77.0
Japan	817	10.4	38.8	26.7	13.0	4.3	0.0	93.1
South Korea	123	4.9	15.4	4.1	12.2	46.3	0.8	83.7
Taiwan	137	1.5	27.7	8.0	31.4	24.1	0.0	92.7
Europe								
Austria	163	3.7	5.5	1.2	0.0	0.0	0.0	10.4
Belgium	137	7.3	23.4	4.4	3.6	2.2	0.0	40.9
Eire	117	2.6	12.8	6.0	4.3	0.9	0.0	26.5
France	216	6.9	17.1	6.5	20.8	19.4	0.9	71.8
Germany	623	2.6	9.3	1.6	0.2	0.2	0.0	13.8
Hungary	71	2.8	7.0	18.3	8.5	9.9	0.0	46.5
Italy	267	2.6	27.7	6.7	1.5	1.1	0.0	39.7
The Netherlands	59	1.7	8.5	0.0	0.0	0.0	0.0	10.2
Poland	76	5.3	13.2	5.3	2.6	3.9	0.0	30.3
Portugal	85	2.4	12.9	1.2	2.4	3.5	0.0	22.4
Russia	87	0.0	2.3	0.0	0.0	2.3	0.0	4.6
Spain	524	5.7	26.9	11.3	3.8	10.3	0.6	58.6
Sweden	75	0.0	4.0	5.3	0.0	0.0	0.0	9.3
Switzerland	104	1.9	13.5	1.9	1.9	2.9	0.0	22.1
Turkey	71	8.5	23.9	2.8	4.2	8.5	0.0	47.9
UK	104	0.0	2.9	0.0	0.0	1.0	0.0	3.8
Oceania								
Australia	128	1.6	8.6	1.6	0.8	5.5	0.0	18.0
Indonesia	0	NA	NA	NA	NA	NA	NA	NA
Global[b]								
	6320	**4.8**	**13.6**	**9.2**	**6.3**	**7.7**	**0.2**	**41.8**

a Drugs under study are benzylpenicillin (penicillin G), cefuroxime, erythromycin, clindamycin, telithromycin, quinupristin/dalfopristin, levofloxacin, tetracycline and co-trimoxazole (trimethoprim/sulfamethizole).

b Global figures for the whole collection; the table illustrates data for selected countries.

MDR = multidrug resistant; **NA** = not available.

vaccination. The rate of antimicrobial-resistant invasive pneumococcal infections was indeed decreased in young children and older individuals after the introduction of the 7-valent paediatric conjugate vaccine in the US. However, as suspected at the time of starting vaccination campaigns,[94] this was accompanied by an increase in invasive disease caused by serotypes not included in the vaccine, some of them also being MDR.[95-97] Currently, health authorities in many European countries have intro-

duced this vaccine into their childhood immunisation programmes, but data documenting the consecutive evolution in resistance rates in Europe are not yet available.

2. Current Therapeutic Options for Multidrug-Resistant (MDR) *S. pneumoniae*

2.1 Clinical Implication of Antimicrobial Resistance

The impact of antimicrobial resistance on clinical outcome in patients with pneumococcal pneumonia or invasive pneumococcal disease remains a controversial issue. The guidelines recently released by the European Respiratory Society[98] and the Infectious Diseases Society of America/American Thoracic Society[99] consensus guidelines on the management of CAP have, nevertheless, both taken antimicrobial resistance issues into consideration.

2.1.1 Penicillin Resistance

For pneumonia, only one report documents treatment failure of parenteral β-lactams in patients infected by resistant pneumococci,[100] but the number of patients included, and in particular the microbiologically-assessable subgroup, was quite small. A meta-analysis also concluded that penicillin non-susceptibility was associated with a higher short-term mortality rate in hospitalised patients with pneumococcal disease, after adjustment for age, comorbidities and severity of illness.[101] However, inadequate antimicrobial therapy did not appear to have contributed to the higher mortality in the penicillin non-susceptible group, so that the authors concluded that penicillin non-susceptibility must rather be considered as a prognostic factor, and that other factors may have a stronger influence on the outcome.[102-104] Two reports also concluded that an initial discordant monotherapy with β-lactams was not associated with an increased mortality or clinical or bacteriological failures.[105,106]

These observations have lead to the conclusion that current antibacterial regimens are still effective in the treatment of penicillin-non-susceptible pneumococcal pneumonia with or without bacteraemia. Pharmacokinetic/pharmacodynamic (PK/PD) considerations may provide an explanation for these findings. Serum antibacterial concentrations of adequately administered β-lactams do indeed exceed the MIC values of all penicillin non-susceptible and most penicillin-resistant pneumococci for at least 40–60% of the administration interval (see table IV for MIC distribution, and table V for pharmacokinetic and pharmacodynamic parameters). Only pneumococci with a penicillin MIC >4 mg/L may become problematic from a PK/PD point of view.[107-109]

For meningitis, penicillin non-susceptibility has been associated with poor outcome in some patients but not in others,[166-168] and it proved to be an independent determinant of mortality.[169] PK/PD target attainment in the infected compartment is again probably critical, but difficult to evaluate, because the penetration of the antibacterial in the cerebrospinal fluid is influenced by the inflammation status and the addition of corticosteroids.[170]

Current guidelines on empirical treatment of bacterial meningitis, therefore, recommend the addition of vancomycin to a third-generation cephalosporin in regions with emergent penicillin or cefotaxime non-susceptible pneumococci.[171]

2.1.2 Macrolide Resistance

Several observational studies reported breakthrough bacteraemia and failure of macrolide treatment in patients with erythromycin-resistant pneumococcal bacteraemia.[172-174] The increased risk of macrolide failure occurred irrespective of the underlying resistance mechanism as soon as the erythromycin MIC is >1 mg/L. However, other authors[175] questioned the clinical relevance of *in vitro* macrolide resistance, in particular for low-level resistance due to the efflux.

On the basis of accumulating reports of failure with macrolides-azalides in the treatment of pneumococcal pneumonia due to resistant strains,[109,176] the updated European and American guidelines recommend not to use macrolides as monotherapy anymore for the empirical treatment of CAP, especially in areas with high-resistance rates.[98,99]

2.1.3 Fluoroquinolone Resistance

Several well documented reports of treatment failure with fluoroquinolones (ciprofloxacin, levofloxacin) in patients with fluoroquinolone-resistant pneumococcal disease have gained the attention of

Table IV. *In vitro* activity of reference drugs and molecules in development showing activity on *Streptococcus pneumoniae* (for the chemical structures of these compounds, please see the supplementary material ['ArticlePlus'] at http://drugs.adisonline.com)

Drug	Stage of development	Current target indications[a]	Resistance phenotype	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	Reference
β-Lactams							
penicillin	Reference drug		PenS	0.016	0.03	0.016–0.06	110
			PenI	0.25	1	0.12–1	110
			PenR	2	4	2– >16	110
amoxicillin	Reference drug		PenS	≤0.016	0.03	≤0.016–0.12	110
			PenI	0.25	2	0.016–4	110
			PenR	2	8	0.03–16	110
cefuroxime	Reference drug		PenS	0.03	0.12	0.016–0.25	110
			PenI	0.5	4	0.03–4	110
			PenR	4	16	1– >64	110
ceftriaxone	Reference drug		PenS	0.016	0.03	0.016–0.12	110
			PenI	0.25	1	0.016–1	110
			PenR	1	2	0.12–32	110
cefotaxime	Reference drug		PenS	0.016	0.03	0.016–0.12	110
			PenI	0.25	1	0.016–1	110
			PenR	1	2	0.12–32	110
cefditoren	Approved	SSTI, *pharyngitis, AECB, CAP*	PenS	≤0.03	≤0.03	≤0.03–0.06	111
			PenI	0.25	0.5	≤0.03–1	111
			PenR	0.5	0.5	0.12–2	111
ceftobiprole	Phase III	SSTI, VAP, *CAP*	PenS	≤0.015	≤0.015	0.008–0.03	112
			PenI	0.06	0.12	≤0.008–1	112
			PenR	0.25	1	0.015–4	112
cefmatilen (S-1090)	Phase III[b]			0.063	1	0.004–1	113
ceftaroline	Phase II	SSTI, *CAP*	PenS	≤0.016	≤0.016	≤0.016–0.06	114
TAK-599			PenI	0.03	0.06	0.016–0.12	114
(PPI-0903)			PenR	0.12	0.25	0.06–0.5	114
RWJ-54428 (MC-02479)	Phase II[c]		PenS	≤0.015	≤0.015	≤0.008–0.06	112
			PenI	0.125	0.25	0.015–025	112
			PenR	0.5	1	0.125–1	112
faropenem	Phase III	*Sinusitis, AECB, CAP*, SSTI	PenS	0.008	0.25	≤0.004–2	112
			PenI	≤0.004	0.008	≤0.004–0.12	112

Continued next page

Table IV. Contd

Drug	Stage of development	Current target indications[a]	Resistance phenotype	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	Reference
			PenR	0.5	1	≤0.004–2	112
tomopenem	Phase II	Nosocomial	PenS	≤0.03	≤0.03	≤0.03	115
(CS-023;		pneumonia	PenI	0.06	0.12	0.03–0.25	115
RO4908463)			PenR	0.12	0.25	0.06–0.5	115
Glycolipopeptides							
vancomycin	Reference drug		PenS	0.5	0.5	0.1–0.5	116
			PenR	0.25		0.25–2	116
oritavancin	Phase III	SSTI, bloodstream	PenS	≤0.002	0.008	≤0.002–0.06	116
			PenR	≤0.002		≤0.002–0.06	116
telavancin	Phase III (HAP)	SSTI, *HAP*	PenS	0.016	0.016	0.008–0.03	117
			PenR				
dalbavancin	Phase III	SSTI, bloodstream	PenS	0.03	0.06	0.016–0.13	116
			PenR	0.03		0.008–0.13	116
daptomycin	Approved	SSTI	PenR		≤0.125	≤0.125	118
MX-2401	Preclinical	*Gram-positive infections*				0.125–2	119
Macrolides							
clarithromycin	Reference drug		ML-S	0.03	0.06	≤0.016–0.5	110
			ML-R	>16	>16	0.25–64	110
azithromycin	Reference drug		ML-S		0.125	0.125–2	120
			ML-R		128	2–128	120
Ketolides							
telithromycin	Approved	*CAP* (*AECB*, and	ML-S	0.004	0.008	≤0.015	121
		sinusitis; withdrawn for these indications in the US[122]).	ML-R	0.015	0.12	≤0.002–0.5	121
cethromycin	Phase III	*CAP, bronchitis,*	ML-S	0.001	0.002	≤0.004	121
		pharyngitis and sinusitis	ML-R	0.004	0.015	≤0.002–1	121
EDP-420	Phase II	*CAP*	ML-S	0.03	0.03	≤0.015–0.5	123
			ML-R	0.06	0.5	≤0.015–2	123
FMA1485	preclinical	*RTIs*	ML-S		0.03		124
			ML-R		0.06		124
Lincosamides							
clindamycin	Reference drug			≤0.25	≤0.25	≤0.25	125

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Table IV. Contd

Drug	Stage of development	Current target indications[a]	Resistance phenotype	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	Reference
VIC105555	Preclinical			0.03	0.03	≤0.016–0.03	125
Streptogramins							
quinupristin/	Approved	SSTI	ML-S	0.25	0.5	0.25–0.5	126
dalfopristin			ML-R	0.5	1	0.125–2	126
Oxazolidinones							
linezolid	Reference drug	SSTI, HAP, *CAP*	PenR	1	2	0.5–4	127
ranbezolid	Phase I, dropped off?	Nosocomial infections	PenR	0.5	1	0.06–2	127
Tetracyclines							
tetracycline	Reference drug		Tet-S	0.5		0.25–2	112
			Tet-R	64		8–128	112
doxycycline	Reference drug			0.25	0.5	≤0.25–32	33
Glycylcyclines							
tigecycline	Approved	SSTI, IAI, off-label:	Tet-S	0.25		0.12–0.5	112
		pneumonia caused by MDR organisms	Tet-R	0.12		0.06–0.5	112
MK-2764	Phase I/(II)	Community-acquired	Tet-S	0.06	0.12	0.016–0.25	128
		and complicated infections of the skin and *pneumonia*	Tet-R			≤0.06	129
Quinolones							
levofloxacin	Reference drug	*RTIs*, SSTI, UTIs	Q-S	1	1	0.25–2	112
			Q-R	8	16	1–32	112
moxifloxacin	Reference drug	*CAP, AECB,*	Q-S	0.12	0.25	0.03–0.25	130
		sinusitis	Q-R	2	4	2–4	130
gemifloxacin	Reference drug	*CAP, AECB*	Q-S	0.03	0.03	0.008–0.06	130
			Q-R	0.25	0.25	0.12–4	130
garenoxacin	Phase III completed	*RTIs*, pelvic	Q-S	0.03	0.03	≤0.016–0.06	131
		inflammation	Q-R	0.25	1	0.03–1	131
sitafloxacin	Phase III phototoxicity		Q-S	0.06	0.12	≤0.008–0.5	112
			Q-R			0.25–1	112
WCK-771A	Phase II	MRSA	All isolates	0.25	0.5	0.06–1	132
			Q-R	4	16	0.25–16	132
WCK-1152	Phase I	*RTIs*	All isolates	0.03	0.06	0.016–0.125	132

Continued next page

Table IV. Contd

Drug	Stage of development	Current target indications[a]	Resistance phenotype	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	Reference
			Q-R	0.25	1	0.06–1	132
WCK-1153	Preclinical		All isolates	0.016	0.03	0.016–0.06	132
			Q-R	0.125	0.5	0.016–0.5	132
DX-619	Phase I		All isolates	0.007	0.03	0.002–0.6	133
			Q-R	0.03	0.25	0.015–0.5	134
DK-507K	Phase I		Q-S	0.06	0.125	0.03–0.25	135
	(discontinued for mild toxicity)		Q-R	0.25	0.5	0.25–1	135
DC-159a	Preclinical	*RTIs*	All isolates	0.12	0.12		136
			Q-R	1	2		136
DW-224a	Preclinical		Q-S	0.016	0.03	0.004–0.03	130
			Q-R	0.12	0.25	0.06–1	130
PGE 9262932	Preclinical		Q-S	≤0.015	≤0.015	≤0.015–0.5	137
			Q-R	0.06	0.12	≤0.015–0.5	137
olamufloxacin (HSR-903)				0.06	0.12	≤0.03–0.12	138
Diaminopyidine							
trimethoprim	Reference drug				>128		139
iclaprim	Phase III	SSTI			4		139
AR-709	Preclinical	*Upper and lower RTIs*	MDR	0.25	0.5	≤0.03–1	140
Deformylase inhibitors							
LBM415	Phase I	*RTIs*	PenR	0.5	1	0.06–4	141
			ML-R	0.5	4	0.016–16	141

a Indications where *S. pneumoniae* can be a causative agent are highlighted in italic characters.

b Last publication on this drug: 2002.

c Last publication on this drug: 2003.

AECB = acute exacerbation of chronic bronchitis; **CAP** = community-acquired pneumonia; **HAP** = hospital-acquired (nosocomial) pneumonia; **IAI** = intra-abdominal infection; **MIC_{50}/MIC_{90}** = minimum concentration to inhibit growth of 50%/90% of isolates; **MDR** = multidrug resistant; **ML-R** = macrolide-lincosamide resistant; **ML-S** = macrolide-lincosamide sensitive; **MRSA** = methicillin-resistant *Staphylococcus aureus*; **PenI** = penicillin intermediate; **PenR** = penicillin resistant; **PenS** = penicillin sensitive; **Q-R** = quinolone resistant; **Q-S** = quinolone sensitive; **RTIs** = respiratory tract infections; **SSTI** = skin and soft tissue infection; **Tet-R** = tetracycline resistant; **Tet-S** = tetracycline sensitive; **VAP** = ventilator-associated pneumonia.

Table V. Pharmacokinetics and pharmacokinetic/pharmacodynamic (PK/PD) parameters of current drugs and molecules in clinical stage of development for *Streptococcus pneumoniae* infections

Drug	Proposed dosage	C_{max} (mg/L)	$t_{1/2}$ (h)	AUC (mg • h/L)	Protein binding (%)	PK/PD parameter[a]	PK/PD break-point	Adequateness of PK/PD breakpoint with current MIC distributions	References
β-Lactams									
amoxicillin	500mg tid PO	5–11	1	13	17	fT >MIC[b] = 50% fT >MIC = 100%	2 0.2	= MIC_{50} PenR = MIC_{50} PenI	142,143
	1000mg tid IV	100	1	120	17	fT >MIC = 50% fT >MIC = 100%	2 0.2	= MIC_{50} PenR = MIC_{50} PenI	143,144
	1000mg qid IV	100	1	160	17	fT >MIC = 50% fT >MIC = 100%	4 0.6	>MIC_{50} PenR >MIC_{50} PenI	143,144
cefuroxime axetil	500mg bid PO	8	1.2	23	33	fT >MIC = 50% fT >MIC = 100%	0.5 0.01	= MIC_{50} PenI <MIC_{50} PenS	145
ceftriaxone	1g od IV	130	6	1006	90–95	fT >MIC = 50% fT >MIC = 100%	2 1	= MIC_{90} PenR = MIC_{50} PenR	143,146
	2g od IV	257	6	1703	90–95	fT >MIC = 50% fT >MIC = 100%	5 2	>MIC_{90} PenR = MIC_{90} PenR	143,146
cefotaxime	1g tid IV	102	1	200	30–50	fT >MIC = 50% fT >MIC = 100%	2 0.25	= MIC_{90} PenR = MIC_{50} PenI	143,147
	2g tid IV	214	1	400	30–50	fT >MIC = 50% fT >MIC = 100%	4 0.5	>MIC_{90} PenR = MIC_{50} PenI	143,147
cefditoren	400mg bid PO	4–5	1.3	14	88	fT >MIC = 50% fT >MIC = 100%	0.02 0.001	= MIC_{90} PenS <MIC_{50} PenS	143,148
ceftobiprole	500mg bid IV	35.5	3.4	150	48	fT >MIC = 50% fT >MIC = 100%	5 1	>MIC_{90} PenR = MIC_{90} PenR	143,149
ceftaroline	600mg bid IV	19	1.6	56	<20	fT >MIC = 50% fT >MIC = 100%	1 0.1	>MIC_{90} PenR >MIC_{90} PenI	143,150,151
faropenem	300mg bid PO	13.8	1.31	50	90	fT >MIC = 20% fT >MIC = 100%	0.2 0.03	>MIC_{90} PenI >MIC_{90} PenI	112,152
Glycolipopeptides									
vancomycin	15 mg/kg bid IV	20–50	4–8	260	10–55	fAUC/MIC >400	0.3	>MIC_{50}	143,153
telavancin	7.5–10 mg/kg od IV	88	7–9	762	93	fAUC/MIC >10–20	4–2	>MIC_{90}	154,155
Macrolides									
clarithromycin	500mg bid PO	2.1	4.3	14	70	fAUC/MIC >25	0.2	>MIC_{90} ML-S	143,156
azithromycin	500mg od PO	0.4	40–68	3.4	7–50	fAUC/MIC >25	0.1	= MIC_{90} ML-S	143,157,158
Ketolides									
telithromycin	800mg od PO	1.2	13	6	89	fAUC/MIC >25	0.02	>MIC_{90} ML-S = MIC_{50} ML-R	143,159,160

Continued next page

Table V. Contd

Drug	Proposed dosage	C_{max} (mg/L)	$t_{1/2}$ (h)	AUC (mg • h/L)	Protein binding (%)	PK/PD parameter[a]	PK/PD break-point	Adequateness of PK/PD breakpoint with current MIC distributions	References
cethromycin	150mg od PO	0.18	4.9	0.9	86–96	fAUC/MIC >25	0.003	= MIC_{90} ML-S = MIC_{50} ML-R	143,161
Oxazolidinones									
linezolid	600mg bid PO	13	3.5	180	31	fAUC/MIC >50	4	>MIC_{90}	162,163
Tetracyclines									
doxycycline	100mg od PO	1.7	14	40	82–93	fAUC/MIC >25	0.2	<MIC_{50}	143,164
	200mg od PO	5.2	13	90	82–93	fAUC/MIC >25	0.5	= MIC_{90}	143,164
Glycylcyclines									
tigecycline	50mg bid IV	0.5–0.6	37	5	79	AUC/MIC >12	0.5	>MIC_{50} Tet-R	164
Fluoroquinolones									
levofloxacin	500mg od PO	5	7	48	31	fC_{max}/MIC >8 fAUC /MIC >25 fAUC/MIC >125	0.4 1.5 0.3	<MIC_{50} Q-S >MIC_{90} Q-S <MIC_{50} Q-S	143,165
	750mg od PO	7	7	82	31	fC_{max}/MIC >8 fAUC /MIC >25 fAUC/MIC >125	0.6 2 0.4	<MIC_{50} Q-S >MIC_{90} Q-S <MIC_{50} Q-S	143,165
	500mg bid PO	5	7	96	31	fC_{max}/MIC >8 fAUC /MIC >25 fAUC/MIC >125	0.4 3 0.5	<MIC_{90} Q-S >MIC_{90} Q-S <MIC_{50} Q-S	143,165
moxifloxacin	400mg od PO	3.4	12	34	47	fC_{max}/MIC >8 fAUC /MIC >25 fAUC/MIC >125	0.2 0.5 0.2	= MIC_{90} Q-S >MIC_{50} Q-R >MIC_{90} Q-S	143,165
gemifloxacin	320mg od PO	1.2	8	10	60	fC_{max}/MIC >8 fAUC /MIC >25 fAUC/MIC >125	0.05 0.1 0.02	>MIC_{90} Q-S >MIC_{90} Q-S = MIC_{90} Q-S	143,165
garenoxacin	400mg od PO	5	14.2	60	75	fC_{max}/MIC >8 fAUC /MIC >25 fAUC/MIC >125	0.15 0.5 0.12	>MIC_{90} Q-S >MIC_{50} Q-R >MIC_{90} Q-S	143,165

a Breakpoint determined based on parameters predictive of antibacterial efficacy, as listed in the column. In some cases, two or three values are proposed, which correspond to the parameter for efficacy in immunocompetent patients and in immunocompromised patients or severe infections, respectively.

b Percentage of dosing interval that free drug concentrations remain above MIC.

AUC = area under the plasma/serum concentration-time curve; **bid** = twice daily; **C_{max}** = maximum plasma/serum concentration; **f** = free fraction of drug; **IV** = intravenous; **MIC** = minimum inhibitory concentration; **ML-R** = macrolide-lincosamide resistant; **ML-S** = macrolide-lincosamide sensitive; **od** = once daily; **PenI** = penicillin intermediate; **PenR** = penicillin resistant; **PenS** = penicillin sensitive; **PO** = orally; **qid** = four times daily; **Q-R** = quinolone resistant; **Q-S** = quinolone sensitive; **T** = time; **Tet-R** = tetracycline resistant; **tid** = three times daily; **$t_{1/2}$** = half-life.

Table VI. Risks factors for multidrug-resistant (MDR) *Streptococcus pneumoniae* infection and strategies for limiting their impact[99,188-190]

Factors associated with carriage or infection by MDR *S. pneumoniae*		Strategies to implement
Host factors	Age (<2–5 and >65y)	Vaccination
	Co-morbidities	Global assessment of the patient
	Immunosuppression	
Environment factors	Geographic area with high-antibacterial consumption	Politics of restricted antibiotic use; promotion of guidelines
	High-population density, life in collectivity (daycare centres for children)	Hygiene
Drug-related factors	Administration of antibacterials in the previous weeks/ months	Diagnostic methods for identification of bacterial infections
	Inappropriate antibacterial treatment in terms of: a) antibacterial choice (risk for MDR: macrolides >cephalosporins >penicillins) b) treatment duration c) antibacterial dosage	a) use of local resistance data; avoiding the use of macrolides; critical appraisal of the interest of new drugs. b) treatment duration as short as possible (5 days) c) optimisation of antibacterial dosages based on pharmacodynamic criteria; selection of antibacterials with higher PK/PD index within a class

PK/PD = pharmacokinetic/pharmacodynamic.

the medical community.[176,177] The level of *in vitro* fluoroquinolone resistance in pneumococci is still low (table II); however, physicians have to be vigilant for clinical failure especially in patients with comorbid illnesses, such as chronic obstructive pulmonary disease and a history of recent fluoroquinolone use.

The European and American guidelines advocate considering respiratory fluoroquinolones only as first-line agents in regions with clinically relevant resistance rates against the first-choice agents or in patients with major intolerance or allergy to the preferred antibacterials. Potent molecules with MIC values several dilutions below the breakpoint (see table V for pharmacodynamic breakpoints), should be preferred to minimise the risk of selecting first-step mutants. [14] Misuse of respiratory fluoroquinolones as a result of incorrect indication, dose and duration must be avoided since it may drive the emergence of higher level resistance.[98,99]

2.2 Combination Therapy

The use of combination therapy for severe (often bacteraemic) pneumococcal pneumonia remains controversial. Evidence in favour of β-lactam plus macrolide combination therapy comes from retrospective observational studies with an inherent risk of bias,[178-180] and is therefore controversial.[181,182] No benefit in survival or clinical efficacy of combining a β-lactam with an antibacterial active against atypical pathogens in non-severe CAP was reported in a meta-analysis[183] or Cochrane analysis.[184] Prospective cohort studies could also not provide a clear answer.[185-187] The discussion is still more complex when considering the option of fluoroquinolone monotherapy instead of a β-lactam plus macrolide.

However, it is noteworthy that all these studies were focused on the importance of broadening the spectrum to atypical pathogens, and not on the interest of combining drugs in empirical treatment for covering resistant strains.

2.3 Current Treatment of MDR *S. pneumoniae* Infections

Table VI lists the main determinants associated with MDR *S. pneumoniae* carriage or infection and the strategies that need to be implemented to avoid their spread.[99,188-191] Among the most important factors, the recent use of antibacterials not only increases the risk of individual carriage and, therefore, of transmission, but also of developing invasive illness. This is probably as a result of the unmasking of minority MDR subpopulation upon antibacterial exposure.[192] Key strategies for limiting further spread of MDR clones are through politics aimed at restricting the global consumption of antibacterials and at promoting their rational use. This implies the selection of more potent molecules within a drug family and the administration of appropriate dosages based on pharmacodynamics.

Table VII. Current therapeutic recommendations for community-acquired pneumonia (CAP) caused by multidrug-resistant (MDR) or non-MDR *Streptococcus pneumoniae* (based on;[98,99] see for appropriate dosages)

Type of infection	European guidelines	American guidelines
CAP, outpatient	Amoxicillin or tetracycline Alternatives: amoxicillin/clavulanic acid, macrolide, respiratory fluoroquinolone	No risk factor for MDR: macrolide or doxycycline Risk factor for MDR or >25% ML resistance: respiratory fluoroquinolone; amoxicillin + macrolide; amoxicillin/clavulanic acid Alternatives to amoxicillin: ceftriaxone; cefuroxime Alternative to macrolide: doxycycline
CAP, inpatient	Penicillin ± macrolide Alternatives to penicillin: amoxicillin; amoxicillin/clavulanic acid; ceftriaxone; cefuroxime; ertapenem (in case of risk of co-infection by Gram-negative pathogens other than *Pseudomonas aeruginosa*) Alternative: respiratory fluoroquinolone PenI: high doses of amoxicillin; ceftriaxone; cefotaxime; respiratory fluoroquinolone; telithromycin PenR: respiratory fluoroquinolone; glycopeptide; linezolid	Respiratory fluoroquinolone, cefotaxime, ceftriaxone, ampicillin + macrolide Alternative to macrolide: doxycycline

ML = macrolide-lincosamide; **PenI** = penicillin intermediate; **PenR** = penicillin-resistant.

Therefore, current therapeutic options for antibacterial-resistant pneumococcal disease still rely upon adequately administered penicillins, aminopenicillins or third-generation cephalosporins (table VII).[190,191] The exception is meningitis, where a combination of a third-generation cephalosporin and vancomycin is recommended in regions with emergent penicillin or cephalosporin non-susceptible pneumococcal strains (table VIII). Monotherapy with macrolides can no longer be recommended because of increasing resistance rates associated with clinical failure. A β-lactam plus macrolide combination is preferred by most authors for severe bacteraemic pneumococcal pneumonia, but it is still matter of debate for moderate pneumonia. Respiratory fluoroquinolones offer a valid alternative for respiratory pneumococcal infection with or without bacteraemia. Additional studies are needed to explore whether monotherapy with a respiratory fluoroquinolone is as good as a combination therapy of β-lactam plus coverage for atypical pathogens in severe CAP.

For MDR pneumococcal infections, respiratory fluoroquinolones and ketolides appear as useful alternatives,[191] mainly based on their *in vitro* activity against penicillin-resistant, macrolide-resistant or MDR pneumococci (table IV), and on clinical trials in which resistant organisms where specifically examined.[6,165,193] However, it must be noted that the use of telithromycin, the first marketed ketolide, is now restricted in the US the single indication of CAP of mild to moderate severity, as a result of severe hepatic toxicity associated with its use,[122] and that neither a paediatric dosage nor an intravenous formulation are available so far.

3. New Drugs in Development for *S. pneumoniae* Infections

Because of the increasing problem of MDR in Gram-positive organisms, research of new molecules with improved activity on methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci and MDR pneumococci has been very active over recent years.[194] Table IV shows

Table VIII. Current therapeutic recommendations for meningitis caused by multidrug-resistant or non-multidrug-resistant *Streptococcus pneumoniae*[171]

Phenotype	Antibacterial	Dosage
PenS	Benzylpenicillin (penicillin G)	4×10^6 U IV every 4h
PenI, cephalosporin S	Cefotaxime Ceftriaxone	2g IV every 4–6h 2g IV every 12h
Cephalosporin I-R	Vancomycin + Cefotaxime or Ceftriaxone	15 mg/kg IV every 8–12h 2g IV every 4–6h 2g IV every 12h

I-R = intermediate to resistant; **IV** = intravenous; **PenI** = penicillin intermediate; **PenS** = penicillin sensitive; **S** = sensitive.

the *in vitro* activity of these drugs against pneumococci.

Of note is that all of these molecules, with the exception of deformylase inhibitors, are new derivatives within existing classes of drugs, which have been selected based on improved intrinsic activity. Some of these derivatives are claimed to remain unaffected by existing resistance mechanisms, which is partially true for molecules that possess new modes of action (i.e. new glycopeptides vs vancomycin)[195] and/or new binding sites in the bacterial target (i.e. ketolides vs macrolides).[196] For other families, new derivatives are less susceptible to some resistance mechanisms. This is for instance well described for resistance mediated by efflux pumps, which extrude old quinolones or macrolides more efficiently than new quinolones or ketolides,[197] or for tetracycline resistance mediated by ribosomal protection, which does not affect glycylcyclines.[198] This is not surprising, since susceptibility to known resistance mechanisms is an integral part of the criteria included in the selection process of new antibacterials for further development. However, in most cases, the emergence of cross-resistance remains inevitable, even though it is not detected by performing MIC determinations, simply because the activity of the drug is so high, even when measured in isolates resistant to the parent compounds, that MIC values remain far below the susceptibility breakpoint. This is well exemplified for new quinolones, which remain active on first-step mutants in topoisomerases.[199,200]

Also of note is that most of these compounds have primarily been designed and selected for an anti-MRSA activity, and proved active against *S. pneumoniae* only during systematic *in vitro* screening. This is probably the consequence of the apparently still satisfying efficacy of current therapeutic options for treating MDR pneumococcal infections (see section 2.3), but the picture may change in a near future.

Focusing on molecules that are now in clinical development and have respiratory tract infections in their target indications, table V summarises the pharmacokinetic data and suggests pharmacodynamic breakpoints. Globally speaking, this table shows that the proposed dosage of all these drugs allows for the pharmacodynamic criteria of efficacy for 90% of the strains susceptible to the parent compounds, and for at least 50% of intermediate or resistant strains to be met.

Within the class of β-lactams, ceftobiprole, ceftaroline and RWJ-54428 are cephalosporins specifically designed to keep activity against MRSA as a result of an increased affinity for PBP2a.[201] Ceftidoren is not active against MRSA. These drugs also show low MIC values against *S. pneumoniae*, including penicillin-intermediate or resistant strains (table IV). Cefditoren has low MIC values but also low time>MIC levels and is also highly protein bound, with correspondingly inappropriate coverage of penicillin non-susceptible strains. Ceftobiprole (as its medocaril prodrug) is currently in phase III trials for complicated skin and skin-structure infections and nosocomial pneumonia due to suspected or proven MRSA, as well as for CAP. The later indication is based on its efficacy at low doses in animal models of pneumonia.[202] The US FDA has granted fast-track status to the compound for these two indications and phase III trial results should be soon available.[203] Ceftaroline (as its fosamil prodrug) is currently being evaluated only for MRSA skin and soft-tissue infections. Both ceftobiprole medocaril and ceftaroline fosamil are limited by having only an intravenous formulation, which restricts their use to hospital. In contrast, cefmatilen is intended for oral administration. Similarly, faropenem medoxomil is an oral carbapenem, which rather directs it towards community usage. Accordingly, it has been evaluated in bacterial rhinosinusitis where 7 days' treatment showed equivalence or superiority to 10 days' treatment with cefuroxime axetil, with fewer gastrointestinal adverse effects than amoxicillin/clavulanic acid.[152] This drug may prove a useful alternative to current β-lactams; however, it would require specific examination of activity against resistant strains and other indications such as CAP.

New glycopeptides have been designed to keep activity against vancomycin-resistant enterococci and staphylococci. Their capacity to interact and to destabilise the bacterial membrane confers them with a highly bactericidal potential towards Gram-positive organisms.[195] However, at the present time, and despite low MIC values against pneumococci (table IV), these drugs are currently in development for MRSA infections only, including hospi-

tal-acquired pneumonia for telavancin. The same development plan holds true for linezolid, which proved efficient against pneumococci, but is indicated only for MRSA infections. However, phase III studies have been performed in CAP, where the drug proved as effective as cephalosporins, with a trend to superior clinical cure rate in patients with bacteraemia.[204,205]

The role of macrolides in pneumococcal infections is severely restricted by the increasing rate of resistance, but ketolides may offer an appropriate alternative, in the sense that they are less affected than conventional macrolides by the most common resistance mechanisms.[6] Thus, their dual-binding site in the ribosome (domains II and V of 23S RNA) allows them to bind with sufficient affinity to ribosomes mutated in the unique binding site (domain V) of conventional macrolides and to impair protein synthesis.[196] They are also poor substrates of macrolide efflux pumps.[206] The development of resistance to ketolides has long been considered as unlikely in terms of fitness cost (are two mutations within a single target viable?).[207] Nevertheless, case reports are beginning to appear all over the world,[208-210] indicating that prudent use is the rule, as for any antimicrobial. Other pros and cons to balance for these drugs are on the one hand, a concomitant activity against intracellular pathogens, which may be useful in empirical therapy, but on the other hand, a severe hepatic toxicity, which recently led the FDA to restrict the indications of telithromycin to CAP.[122] This point will certainly be examined with caution for forthcoming ketolides such as cethromycin.

Even though not registered in this indication, tigecycline might become one alternative of choice for MDR pneumococci. Like most cephalosporins, it can be administered by the intravenous route only.[164] The absence of cross-resistance with currently available anti-pneumococcal or anti-MRSA antibacterials pushed the FDA to authorise the off-label use of this drug for MDR pneumonia. New compounds, such as MK 2764 (PTK 0796), are being developed as oral and intravenous formulations in parallel,[211] which will extend the indications to non-hospitalised patients.

The quinolones represent the class of drugs for which respiratory tract infections are in the forefront of target indications. In this context, the main interesting properties of new fluoroquinolones consist of: (i) once-daily administration; (ii) easy parenteral-oral switch as a result of excellent bioavailability; (iii) spectrum of activity covering bacteria responsible for typical and atypical pneumonia; and (iv) a rapid bactericidal effect. However, several drawbacks temper these advantages. First, they possess a broad spectrum of activity, so that their use will be associated with flora disturbance and selection of resistance in streptococci as well as other bacterial species. Second, these drugs can induce a series of severe adverse effects,[2] which have been associated with restriction of use or total withdrawal of many representatives in the class.[212] The most recent voluntary withdrawals following FDA warnings concern grepafloxacin (cardiovascular events[213]), and gatifloxacin (hypo- and hyperglycaemia[214-216]) and the most recent restricted use was trovafloxacin (hepatotoxicity [217,218]). Third, fluoroquinolones are associated with a number of drug interactions, which either alter the pharmacokinetics of the fluoroquinolone or of the co-administered drug, or increase the risk of adverse effects.[165,212] On these bases, one can easily understand that the development of new fluoroquinolones goes through a careful and early evaluation of their safety profile, causing the arrest of the development of many promising compounds.

4. Conclusion

Currently, the management of infections caused by MDR pneumococci can still continue to be based on use of classical antibacterial choices (β-lactams, ketolides, fluoroquinolones). The success rate will be determined by the correct appraisal of pharmacodynamic parameters, which involve not only the use of appropriate dosages, but also the selection of the more potent agents in the class.

However, in a world of active research, where new, highly potent molecules will soon arrive on the

2 The issue of quinolone toxicity is so topical that a website (http://www.fqresearch.org/index.htm) is devoted to the follow-up of adverse events and changes brought to package inserts as a consequence of pharmacovigilance studies.

market, a burning question concerns the place these molecules could occupy in our future therapeutic arsenal.[219] As long as the total antimicrobial consumption stays flat, these new antibacterials would reduce the utilisation of current drugs, and hence, avoid further increase in resistance. But a non-negligible risk exists that the introduction of new molecules renews the confidence of clinicians in the success of antibacterial therapy and stimulates their wide-scale use, which will unavoidably lead to the development of new resistance mechanisms.

Vaccination remains an interesting alternative to reduce the risk of developing infection; however, the limitation of this approach consists in the difficulty to include the most prevalent serotypes, which can result in the selection of non-vaccinal MDR clones.

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