ELSEVIER

Recently approved and investigational antibiotics for treatment of severe infections caused by Gram-positive bacteria

Peter C Appelbaum[1] and Michael R Jacobs[2]

The development of resistance in the major pathogenic Gram-positive genera *Staphylococcus* and *Streptococccus* has led to the need for new agents that are able to overcome existing resistance mechanisms or that have novel mechanisms of action. There is currently a dearth of new agents that are active against resistant bacterial species. Agents that have recently been approved for clinical use include linezolid, the first oxazolidinone in clinical use, daptomycin, the first lipopeptide in clinical use, and telithromycin, a ketolide that is derived from clarithromycin. Agents currently in clinical development include tigecycline, a broad-spectrum intravenous tetracycline, ceftobiprole, a broad-spectrum cephalosporin that has activity against methicillin-resistant staphylococci, DX-619 and WCK-771, which are potent quinolones that have activity against quinolone-resistant staphylococci, oritavancin and dalbavancin, both of which are new glycopeptides, and iclaprim, which is a diaminopyrimidine. Additional agents that are in preclinical development against Gram-positive pathogens include quinoline–naphthyridine agents, which target novel DNA gyrase sites, other novel quinolones that have high potency, peptide deformylase inhibitors, and new lincosamide, oxazolidinone, lipopeptide and cephalosporin derivatives. Misuse of potent new agents will, however, result in the inevitable development of resistance to these agents; responsible use of potent new agents is required to prevent continuation of this vicious cycle.

Addresses
[1] Department of Pathology, Hershey Medical Center, Hershey, PA 17033, USA
[2] Department of Pathology, Case Western Reserve University and University Hospitals of Cleveland, Cleveland, OH 44106, USA

Corresponding author: Appelbaum, Peter C (pappelbaum@psu.edu)

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Introduction

Gram-positive bacteria such as staphylococci and streptococci have historically been, and still remain, major causes of human morbidity and mortality throughout the world. There are a variety of staphylococcal diseases, for example minor skin pustules, respiratory infections and sepsis, which have a range of outcomes from minor discomfort to death. The main result of *Streptococcus pneumoniae* infection is acute respiratory disease, for example otitis media, pharyngitis, sinusitis and pneumonia, but these and other streptococcal species can also cause skin infections, meningitis and sepsis. Often these diseases cannot be resolved without antimicrobial treatment and they consequently cause much morbidity and mortality in the absence of effective agents. Enterococci are less significant as a cause of disease, although they can cause surgical infections and diseases of the urinary tract; they are mostly of interest as a carrier and transmitter of drug resistance, especially to vancomycin.

Although many of the older antibiotics remain effective, new drug development remains crucial owing to the increase in drug resistance among these important pathogens. This paper will review the effectiveness of some of the recently approved agents and will examine the status of some of those that are currently under investigation.

Resistance patterns in Gram-positive species

Streptococci

Streptococcus pyogenes, the major cause of bacterial pharyngitis, remains fully susceptible to penicillin G. Unfortunately this is not the case for many other pathogenic streptococcal species. On average, worldwide penicillin resistance in *S. pneumoniae* is ~20%, ranging from under 10% in Africa to almost 40% in Asia; nearly one quarter of all US isolates are resistant to penicillin [1•,2]. Amoxicillin and several of the β-lactam agents, particularly ceftriaxone, remain largely effective against *S. pneumoniae*, with the prevalence of resistance generally being much less than 10%. In addition, the respiratory quinolones — levofloxacin, gatifloxacin, moxifloxacin and gemifloxacin — remain highly effective against this species. Trimethoprim–sulfamethoxazole, as well as macrolides and related agents, are becoming increasingly ineffective against *S. pneumoniae*, with overall resistance of about 40% and 25%, respectively, in the US. The resistance of *S. pyogenes* to macrolides varies around the world and has been increasing in recent years, with resistance to erythromycin and azithromycin being as high as 78% in Taiwan in 2001 and with high rates also being reported in parts of Europe, particularly Spain and Italy [3].

Staphylococci

Most staphylococci are resistant to penicillins as they produce β-lactamases, which hydrolyse the β-lactam ring. Methicillin resistance in *Staphylococcus aureus* (MRSA)

and in the coagulase-negative staphylococci (MRCNS) is now common, with almost 35% and 75% of organisms, respectively, being resistant [4]. Methicillin-resistant strains are also resistant to all β-lactams in clinical use, and community-acquired methicillin-resistant *S. aureus* has become a major problem in many countries [5•]. High rates of macrolide resistance have also been reported in Asia and North America; between 1999 and 2001 it was reported that *S. aureus* and CNS have 71.1% and 54.6% resistance to erythromycin, respectively [6,7]. There is much multi-drug resistance amongst the staphylococci, with few drugs being fully active against methicillin-resistant isolates. Resistance to the quinolones that are currently being used occurs amongst virtually all methicillin-resistant *S. aureus*, but also occurs amongst some methicillin-susceptible strains. Until recently, glycopeptides such as vancomycin were one of the few classes of antimicrobials that are active against all staphylococci, but occasional vancomycin-intermediate strains (with minimum inhibitory concentrations [MICs] between 4–8 and 16 mg/ml) have now been found, and three vancomycin-resistant *S. aureus* (VRSA) strains that harbor the *vanA* gene have recently been detected in the USA — there is no reason to expect these to be the last [8•].

Enterococci

Enterococci are largely of interest because of their increasing resistance to vancomycin. There is concern that these resistance genes might be transferred to staphylococci, which would lead to the loss of one of the few drugs that are effective against multidrug-resistant staphylococci [9]. It has been reported that in North America, vancomycin resistance in enterococcal species (VRE) might be as great as 12% [10]. Vancomycin resistance in *Enterococcus faecalis* and *Enterococcus faecium* is usually mediated by way of *vanA* and *vanB* genes, respectively, the former of which also confers resistance to other glycopeptides [8•].

Drug mechanisms and classes

As antibacterial compounds work against bacteria by way of a variety of mechanisms, it is useful to summarize some of these mechanisms as well as to classify the agents by their mechanism of action. Antimicrobial agents act by interfering with cell wall synthesis, cell membrane function, nucleic acid synthesis, ribosomal function and folate synthesis.

Cell wall synthesis can be affected either by preventing the production of new cell walls, effectively stopping the cell from reproducing, or by providing analogues for the bacteria to include as the new cell wall is produced, leading to cell lysis and death. β-lactam drugs such as penicillins, cephalosporins and carbapenems interfere with cell wall production, and glycopeptides such as vancomycin interfere with the cell wall substrate. Although the β-lactams that are currently available are not active against MRSA, investigational cephalosporins, such as ceftobiprole (previously known as BAL-9141 and Ro63-9141) and TAK-599, are active against MRSA [11,12]. Teicoplanin, a glycopeptide agent similar to vancomycin, has been used in Europe for over a decade, but has not yet been approved in the US. It is used in Europe for the treatment of potentially serious bacterial infections caused by Gram-positive bacteria including methicillin-resistant staphylococci [13]. Teicoplanin remains largely effective against staphylococci, although teicoplanin-resistance in CNS of nearly 4% has been reported in Latin America and Asia [4]. New agents in the glycopeptide group include oritavancin and dalbavancin, both of which have good *in vitro* activity against Gram-positive bacteria and are currently in clinical trials, although dalbavancin is not active against enterococci that have VanA-mediated vancomycin resistance [14].

Nucleic acid synthesis can be interrupted by several mechanisms. The antibiotic or a subset of the drug can bind to a site on the DNA, thereby directly blocking replication. Quinolones use this mechanism by binding to DNA gyrase and to topoisomerase II. DNA can also be damaged by antimicrobial agents such as nitroimidazoles. Newer agents that use a similar mechanism but target a different site on the DNA gyrase include the quinoline–naphthyridines and similar agents [15–17]. Quinolone antibiotics under development include WCK-771 [18], WCK-919 and its D-isomer WCK-1153 [19], DX-619 [20], DK-507k [21] and ABT-492 [22].

Ribosomal function can be interrupted by several agents including macrolides, lincosamides, aminoglycosides, tetracyclines and chloramphenicol. Newly discovered members of this group of agents are the ketolides. An example of these is telithromycin, which has been approved for the treatment of bacterial acute exacerbation of chronic bronchitus, acute sinusitis and community acquired pneumonia, including those infections caused by multiple-resistant strains of *S. pneumoniae* [23,24]. Tigecycline, a broad-spectrum glycycline recently approved by the FDA, is potent against streptococci and staphylococci [25,26]. A new lincosamide currently under examination is VIC-105555. In early *in vitro* and *in vivo* pre-clinical trials against Gram-positive and anaerobic bacteria this agent shows promise as a broad-spectrum agent [27,28]. It also appears to have promising pharmacokinetics, with a half-life and clearance profile that compares favorably with clindamycin [29].

Linezolid is an oxazolidinone that affects ribosomal function at a unique site. Bacterial growth is disrupted as this antimicrobial inhibits the initiation process of protein synthesis. It has been approved for treatment of VRE bacteremia, methicillin-susceptible *S. aureus*, MRSA, penicillin-susceptible pneumococcal pneumonia, and skin infections with methicillin-susceptible staphylococci

Table 1

***In vitro* susceptibility of new agents against *Streptococcus pneumoniae*.**

Class	Agent	Development status	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	References
β-Lactam	Ceftobiprole (BAL9141/ 5788, Ro 63-9141)	Clinical	≤0.008–0.12 P^S 0.015–0.5 P^I 0.5–2 P^R	0.015–0.03 P^S 0.25 P^I 0.5 P^R	0.03–0.06 P^S 0.5 P^I 1–2 P^R	[11,36]
β-Lactam	TAK-599	–	≤0.016–0.06 P^S 0.016–0.12 P^I 0.06–0.5 P^R	≤0.016 P^S 0.03 P^I 0.12 P^R	≤0.016 P^S 0.06 P^I 0.25 P^R	[12]
Quinolone	WCK-771	Clinical	–	0.25	0.5	[19]
Quinolone	WCK-919/1153	Pre-clinical	–	0.015	0.03	[37]
Quinolone	DX-619	Pre-clinical	–	–	0.03	[51]
Oxazolidinone	Linezolid	Approved	≤0.03–4	1	1–2	[31,39]
Oxazolidinone	Ranbezolid (RBX 7644)	Pre-clinical	0.06–2	0.25–0.5	0.5–1	[31]
Ketolide	Telithromycin	Approved	0.002–8 ≤0.03–4	– 0.12 $P^{I/R}$	0.12 1 $P^{I/R}$	[23,39,52]
Lincosamide	VIC-105555	Pre-clinical	0.008–0.03[a]	–	0.03[a]	[27]
Streptogramin	Quinupristin/dalfopristin	Approved	≤0.03–8	0.5–1	0.5–2	[37,39]
Glycopeptide	Teicoplanin	Approved	≤0.01–0.25	≤0.01–0.12	≤0.01–0.12	[39,42]
Glycopeptide	Oritavancin (LY33328)	Clinical	≤0.01–0.06	≤0.01	≤0.01	[42]
Glycopeptide	Dalbavancin (BI397)	Clinical	≤0.25	≤0.25	≤0.25	[43]
Lipopeptide	Daptomycin	Approved	≤0.015–1	0.12[b]	0.25	[41]
Diaminopyrimidine	Iclaprim (AR-100)	Clinical	–	1	8	[46]
Glycylcycline	Tigecycline	Clinical	≤0.015–1	≤0.03–0.12	0.06–0.5	[39,26]
PDF-inhibitor	LBM415 (NVP PDF-713)	Pre-clinical	0.06–2	0.5–1	1	[48]

P^I, penicillin-intermediate (MIC values 0.12–1 μg/mL); P^R, penicillin-resistant (MIC values ≥2 μg/mL); P^S, penicillin-susceptible (MIC values ≤0.06 μg/mL).

[a] Data for clindamycin-susceptible isolates.

[b] Modal value.

Table 2

***In vitro* susceptibility of new agents against *Staphylococcus aureus*[a].**

Class	Agent	Development status	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	References
β-Lactam	Ceftobiprole (BAL9141/ 5788, Ro 63-9141)	Clinical	0.25–1 M^S 0.5–4 M^R	0.5 M^S 1–2 M^R	0.5–1 M^S 2–4 M^R	[11,36]
β-Lactam	TAK-599	Preclinical	0.03–0.5 M^S 0.12–2M^R	0.25 M^S 1 M^R	0.25 M^S 2 M^R	[12]
Quinolone	WCK-771	Clinical	≤0.008–>4	≤0.008 Q^S 0.5 Q^R	0.015 Q^S 1 Q^R	[18]
Quinolone	WCK-919/1153	Pre-clinical	–	0.015 Q^S 0.5 Q^R	0.03 Q^S 2 Q^R	[38]
Quinolone	DX-619	Pre-clinical	–	0.008 M^S 0.12 M^R	0.06 M^S 1 M^R 0.5 Q^R	[20,51]
Oxazolidinone	Linezolid	Approved	0.5–4	2	4	[31,38]
Oxazolidinone	Ranbezolid (RBX 7644)	Pre-clinical	0.25–4	2	2	[31]
Ketolide	Telithromycin	Approved	≤0.015–0.25 E^S 0.06–0.5 $E^{R\text{-ind}}$ >128 $E^{R\text{-const}}$ ≤0.015–0.25 $E^{R\text{-msr}}$	0.06 E^S 0.12 $E^{R\text{-ind}}$ >128 $E^{R\text{-const}}$ 0.06 $E^{R\text{-msr}}$	0.12 E^S 0.25 $E^{R\text{-ind}}$ >128 $E^{R\text{-const}}$ 0.12 $E^{R\text{-msr}}$	[40]
Lincosamide	VIC-105555	Pre-clinical	0.125–0.5	–	0.5	[27]
Streptogramin	Quinupristin–dalfopristin	Approved	–	0.25	0.5	[38]
Glycopeptide	Teicoplanin	Approved	≤0.12–8	0.5	1–2	[41]
Glycopeptide	Oritavancin (LY333328)	Clinical	0.12–4	0.5–1	1–2	[42]
Glycopeptide	Dalbavancin (BI397)	Clinical	≤0.015–1	0.03–0.12	0.06–0.25	[14,43]
Lipopeptide	Daptomycin	Approved	≤0.015–1	0.25	0.5	[41]
Diaminopyrimidine	Iclaprim (AR-100)	Clinical	–	0.12	0.5	[47]
Glycylcycline	Tigecycline	Clinical	0.06–2	0.12–0.25	0.25–0.5	[25,26]
PDF-inhibitor	LBM415 (NVP PDF-713)	Pre-clinical	0.015–4	1–2	2–4	[48]

E^S, erythromycin-susceptible; $E^{R\text{-const}}$, erythromycin-resistant, constitutive erm resistance mechanism; $E^{R\text{-ind}}$, erythromycin-resistant, inducible erm resistance mechanism; $E^{R\text{-msr}}$, erythromycin-resistant, msr resistance mechanism; M^R, methicillin-resistant; M^S, methicillin-susceptible; Q^R, quinolone-resistant; Q^S, quinolone-susceptible.

[a] Activity against combined methicillin-susceptible and -resistant isolates are shown unless specified.

[30]. Other oxazolidinone agents currently under development include ranbezolid (RBX-7644) [31], which is currently in pre-clinical development.

Quinopristin–dalfopristin, a combination intravenous streptogramin antibiotic, also inhibits protein synthesis but at a different step. Examples in which this mechanism is used include the treatments of severe infections caused by VRE, nosocomial pneumonia, and infections related to intravascular catheters [32].

Cell membrane function is interrupted by the lipopeptide daptomycin, which has been approved for the treatment of complicated skin and soft tissue infections including those caused by MRSA [33]. It has not been indicated that this is able to treat pneumonia [34].

Finally, folate synthesis, which is necessary for DNA replication, is blocked by sulfonamides and by trimethoprim. Newer agents that use this mechanism include iclaprim (AR-100), which is currently in early clinical trials [35].

In vitro activity

In vitro MIC data for many of the agents discussed in this review are summarized in Tables 1–4. One of the promising agents that is currently in clinical trials is ceftobiprole, which has good *in vitro* activity against Gram-positive species including MRSA [11,36]. The minimum concentration of ceftobiprole that is needed to inhibit 90% of organisms (MIC_{90}) for penicillin-resistant pneumococci is 1 μg/mL and is 2 μg/mL for methicillin-resistant staphylococci. The quinolone agents remain largely effective against pneumococci, although quinolone resistance is found in a small proportion of isolates. Some of the newer quinolones, such as DX-619, WCK-771 and WCK-919, have considerably better *in vitro* activity against quinolone-resistant staphylococci than quinolones that are currently available [19,20,37,38]. It remains to be seen whether pharmacokinetic and pharmacodynamic profiles translate to equally high efficacy *in vivo*.

The new oxazolininone ranbezolid has MIC values similar to linezolid [31]. Telithromycin is considered to be active against macrolide-resistant *S. pneumoniae*, with an MIC_{90} of 1 μg/mL, but MICs are lower against macrolide-susceptible pneumococci [23,39]. Telithromycin is active against macrolide-susceptible staphylococci, with an MIC_{90} of 0.12 μg/mL, but not against constitutively macrolide-resistant staphylococci or against *S. pyogenes*, which are macrolide-resistant owing to the *erm*(B) mechanism [3,40]. Early studies with the new lincosamide VIC-105555 show some promise, with an MIC_{90} of 0.03 μg/mL reported for penicillin-resistant *S. pneumoniae*

Table 3

***In vitro* susceptibility of new agents against coagulase-negative staphylococci[a].**

Class	Agent	Status	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	Reference
β-Lactam	Ceftobiprole (BAL9141/ 5788, Ro 63-9141)	Clinical	0.03–1 M^S 0.25–4 M^R	0.25 M^S 1 M^R	0.5–1 M^S 2 M^R	[11,36]
β-Lactam	TAK-599	Pre-clinical	≤0.06–0.5 M^S 0≤0.06–2 M^R	0.06 M^S 0.25 M^R	0.25 M^S 0.5 M^R	[12]
Quinolone	WCK-771	Clinical	≤0.008–>4	0.015 Q^S 0.5 Q^R	0.03 Q^S 1 Q^R	[18]
Quinolone	WCK-919/1153	Pre-clinical	–	0.015 Q^S 0.5 Q^R	0.03 Q^S 1 Q^R	[38]
Oxazolidinone	Linezolid	Approved	0.5–4	1–2	2–4	[31,38]
Oxazolidinone	Ranbezolid (RBX 7644)	Pre-clinical	≤0.06–1 M^S ≤0.06–4 M^R	0.12 M^S 0.25 M^R	0.5 M^S 1 M^R	[31]
Ketolide	Telithromycin	Approved	0.03–>128	0.06 M^S 0.06	0.12 M^S >128	[23,53]
Lincosamide	VIC-105555	Pre-clinical	–	–	0.5 M^R	[27]
Streptogramin	Quinupristin–dalfopristin	Approved	–	0.25	0.5 Q^S 0.25 Q^R	[38]
Glycopeptide	Teicoplanin	Approved	≤0.12–16 M^S ≤0.12–>32	1[b] M^S 2[b] M^R	4 M^S 8 M^R	[41]
Glycopeptide	Oritavancin (LY333328)	Clinical	≤0.01–2 M^S 0.06–4 M^R	0.5 M^S 1 M^R	2 M^S 2 M^R	[42]
Glycopeptide	Dalbavancin (BI397)	Clinical	≤0.015–0.25	0.03	0.06	[43,44]
Lipopeptide	Daptomycin	Approved	0.03–1	0.25[b]	0.5	[41]
Diaminopyrimidine	Iclaprim (AR-100)	Clinical		0.25	>32	[47]
Glycylcycline	Tigecycline	Clinical	0.06–1	0.25	0.5	[26]
PDF-inhibitor	LBM415 (NVP PDF-713)	Pre-clinical	0.25–2 M^S 0.06–2 M^R	1 M^S 0.5 M^R	1	[48]

[a] Activity against combined methicillin-susceptible and -resistant isolates are shown unless specified.
[b] Modal value Q^R, quinolone-resistant; Q^S, quinolone-susceptible; M^R, methicillin-resistant; M^S, methicillin-susceptible.

Table 4

***In vitro* susceptibility of new agents against vancomycin-susceptible and -resistant enterococci.**

Agent	*Enterococcus faecalis*			*Enterococcus faecium*			References
	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	
Vancomycin-susceptible							
Vancomycin	0.25–4	1	4	0.12–4	1	2	[54]
Teicoplanin	≤0.01–2	0.06	1	≤0.01–1	0.25	0.5	[42]
Oritavancin (LY333328)	0.06–1	0.5	1	≤0.1–0.5	0.06	0.12	[42]
Dalbavancin (BI397)	0.06–0.12[a]	0.06[a]	0.12[a]	–	–	–	[14]
Daptomycin	0.06-4	1	2	≤0.015–4	2	2	[54]
Vancomycin-resistant							
Vancomycin	32–>128	>128	>128	32–>128	>128	>128	[54]
Teicoplanin	64–>128[b]	>128[b]	>128[b]	0.13–8[c]	1[c]	2[c]	[14]
Oritavancin (LY333328)	0.03–2	1	2	0.12–1	1	1	[42]
Dalbavancin (BI397)	0.5–>128[b]	32[b]	>128[b]	0.02–2[c]	0.13[c]	1[c]	[14]
Daptomycin	0.5–4	1	4	0.12–4	2	2	[54]

[a] Data for *E. faecalis* and *E. faecium*.
[b] VanA-resistance mechanism.
[c] VanB-resistance mechanism.

and of 0.5 μg/mL for staphylococci, regardless of methicillin susceptibility; however, activity against clindamycin-resistant isolates has not been published [27]. Quinupristin–dalfopristin, the streptogramin combination agent, has an MIC_{90} of 1 μg/mL against penicillin-resistant *S. pneumoniae*; in recent reports it was shown to have MIC_{90} values of 0.25 μg/mL and 0.5 μg/mL against quinolone-resistant *S. aureus* and CNS, respectively [37,38].

The lipopeptide and glycopeptide agents all show good activity against penicillin-susceptible and penicillin-resistant *S. pneumoniae* and have variable activity against staphylococci. Teicoplanin and the investigational drug oritivancin have MIC_{90} values of 2 μg/mL against methicillin-resistant *S. aureus* and of 1 μg/mL against methicillin-susceptible isolates [41,42]. The activity of oritavancin against CNS is similar to that against *S. aureus*, but the potency of teicoplanin against CNS is lower than against *S. aureus* [41,42]. MIC_{90} values of dalbavancin are 0.13–0.25 mg/L against methicillin-susceptible and methicillin-resistant *S. aureus* and CNS [14,43]. MIC_{90} values of daptomycin against methicillin-susceptible and methicillin-resistant *S. aureus* and CNS are between 0.25 mg/L and 0.5 mg/L [41,44]. A new lipopeptide in pre-clinical development is HMR 1043, which has MIC_{90} values against staphylococci, streptococci and enterococci that range from 0.12–4 μg/mL [45].

Iclaprim has poor activity against *S. pneumoniae*, with an MIC_{90} of 8 μg/mL. It shows some promise against *S. aureus*, with an MIC_{90} of 0.5 μg/mL, but its MIC_{90} against CNS is >32 μg/mL, although the MIC_{50} is 0.25 μg/mL [46,47]. Tigecycline is active against penicillin-susceptible and penicillin-resistant *S. pneumoniae* and methicillin-susceptible and methicillin-resistant staphylococci with MIC_{90} values of 0.25–0.5 μg/mL [25,26]. The experimental peptide deformylase inhibitor LBM415 (NVP PDF-713) is moderately active, with MIC_{90} values for *S. pneumoniae* (regardless of penicillin susceptibility), CNS (regardless of methicillin susceptibility), methicillin-susceptible *S. aureus* and MRSA, respectively, of 1–2 μg/mL, 1–2 μg/mL, 2 μg/mL and 4 μg/mL [48–50]. Further studies of these investigational agents are needed to determine their pharmacokinetic and pharmacodynamic profiles as well as their safety, clinical efficacy and MIC breakpoints.

Conclusions

Although agents that are currently available, such as vancomycin and daptomycin, are active against all pneumococci and almost all staphylococci, their use is limited by the need to administer these agents parenterally, by their inadequate penetration of some body compartments, and by the development of VRSA. The use of oral agents that are currently available has been challenged by the development of pneumococci that are resistant to several drug classes, and, more recently, the development of community-acquired MRSA infections. The introduction of linezolid, a representative of a new class of agents — the oxazolidinones — for oral and parenteral use, and of daptomycin for parenteral use has expanded our treatment options. Several agents in development that have novel mechanisms of action or that have sufficient improvements in potency to overcome resistance also show promise against staphylococcal and pneumococcal infections.

Update

A fourth VRSA strain has recently been isolated in Michigan (JT Rudrick, personal communication) from the toe wound of a diabetic patient. As stated above, tigecycline has recently been approved by the FDA for treatment of intra-abdominal and complicated skin and

soft tissue infections. Since the submission of this review, the oral streptogramin NXL 103 (formerly known as XRP 2868) has been put into preclinical development. This compound is potent against all pneumococci, with MIC values ranging between 0.06 and 1.0 μg/ml [55]. NXL 103 is active against all other Gram-positive bacteria except vanomycin-resistant enterococci [56].

References and recommended reading

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- • of special interest
- •• of outstanding interest

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