REVIEW ARTICLE

Novel pharmaceutical molecules against emerging resistant gram-positive cocci

Authors
Roberto Manfredi, MD[1]
Sergio Sabbatani, MD[1]

[1]Department of Internal Medicine, Aging, and Nephrological Diseases, Division of Infectious Diseases, "Alma Mater Studiorum" University of Bologna, S. Orsola Hospital, Bologna, ItalyDiyarbakir, Turkey.

ABSTRACT

Introduction: methicillin- and also vancomycin (glycopeptide)-resistant Gram-positive organisms have emerged as an increasingly problematic cause of hospital-acquired infections, also spreading into the community. Vancomycin (glycopeptide) resistance has emerged primarily among Enterococci, but the MIC values of vancomycin for the entire *Staphylococcus* species are also increasing worldwide. **Material and Methods:** the aim of our review is to evaluate the efficacy and tolerability of newer antibiotics with activity against methicillin-resistant and glycopeptide-resistant Gram-positive cocci, on the ground of our experience at a tertiary care metropolitan Hospital, and the most recent literature evidences in this field. **Results:** Quinupristin-dalfopristin, linezolid, daptomycin, and tigecycline show an excellent in vitro activity, comparable to the activity of vancomycin and teicoplanin for methicillin-resistant staphylococci, and superior to the one that vancomycin for vancomycin-resistant isolates. Dalbavancin, televancin, and oritavancin are new lipoglycopeptide agents with excellent activity against Gram-positive cocci, and have superior pharmacodynamics properties compared to vancomycin. We review the bacterial spectrum, clinical indications and practical use, pharmacologic properties, and expected adverse events and contraindications associated with each of these novel antimicrobial agents, compared with the present standard of care. **Discussion:** linezolid activity is substantially comparable to that of vancomycin in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia, although its penetration into the respiratory tract is exceptionally elevated. Tigecycline has activity against both *Enterococus* species and MRSA; it is also active against a broad spectrum of *Enterobacteriaceae* and anaerobes, which allows for use intraabdominal, diabetic foot and surgical infections. Daptomycin has a rapid bactericidal activity for *Staphylococcus aureus* and it is approved in severe complications, such as bacteremia and right-sided endocarditis. It cannot be used to treat pneumonia and respiratory diseases, due to its inactivation in the presence of pulmonary surfactant.

Keywords: resistant gram-positive cocci, staphylococci, enterococci, pneumococci, streptococci, epidemiology, clinical issues, novel antimicrobial compounds, characteristics, literature evidences.

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Correspondence to:
Roberto Manfredi, MD
Associate Professor of Infectious Diseases, University of Bologna
c/o Infectious Diseases, S. Orsola Hospital
Via Massarenti 11
I-40138 Bologna, Italy
Tel: +39-051-6363355
Fax: +39-051-343500
E-mail: Roberto.manfredi@unibo.it

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INFECTIONS CAUSED BY GRAM-POSITIVE COCCI. AN OUTLINE OF THEIR ANTIBIOTIC RESISTANCE PROFILE

Gram-positive cocci have re-emerged as predominant pathogens of human hosts within the past 10-15 years. After the introduction of penicillin over 60 years ago, infections by *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* finally became treatable. Within a short period of time, however, *S. aureus* developed resistance to penicillin. As a consequence, penicillinase-resistant penicillins were successfully introduced with in the early 1960's. Concomitantly, resistance emerged for the penicillinase-resistant penicillins, and finally methicillin (oxacillin)-resistant *S. aureus* (MRSA) became a major hospital-acquired pathogen. Vancomycin (belonging to the class of glycopeptides) remained an active agent against MRSA and coagulase-negative Staphylococci, so that it was increasingly used during the subsequent years, until now. From the 1990's to the present, however, the emergence of resistance to vancomycin also occurred in a significant proportion.[1-3] First among these organisms were *Enterococcus faecium* and *Enterococcus faecalis*.[4] Subsequently, vancomycin (glycopeptide)-resistant enterococci (VRE) became a major hospital-acquired pathogen. In the past several years, MRSA were also spreading clonally into the community (the so-called "CA-MRSA"), leading to increased use of vancomycin-teicoplanin therapy.[5] In the late 1990's, glycopeptide resistance was reported for coagulase-negative Staphylococci[6] and then, *S. aureus* (the so-called vancomycin-intermediate *S. aureus*, or VISA, and the so-called glycopeptide-intermediate *S. aureus*, or GISA). The first reported isolation of VISA occurred in Japan in 1997[7] and more than one hundred VISA isolates have been reported in the subsequent years.[8] In the year 2002, three vancomycin-resistant *S. aureus* (VRSA) strains isolated from clinical specimens of American patients were found to have high level resistance to vancomycin (MIC >32 ug/mL).[9] Although a number of cases of VRSA have since been described,[10] these isolates fortunately have not yet become widespread.

The re-emergence of Gram-positive cocci has been well established in the setting of hospital-acquired infections, but community-acquired infections due to MRSA have become increasingly problematic during the last years.[11-13] Foreign body infections and bacteremia caused by coagulase-negative Staphylococci have also increased during time.[14] As a result, vancomycin-teicoplanin usage has increased in both inpatients and outpatients. Although the majority of *S. aureus* strains remain susceptible *in vitro* to vancomycin, its efficacy against methicillin-sensitive *S. aureus* (MSSA) is inferior to that of penicillinase-resistant penicillins and beta-lactam derivatives as a whole.[15,16]

Actually, MRSA is born as a multi-drug resistant pathogen. Resistance to the macrolides, lincosamides, aminoglycosides, and all beta-lactam agents as a group, as well as fluoroquinolones, is also seen when MRSA is of clinical concern. Rifampin should not be used as a single agent due to rapid emergence of resistance in these microorganisms, while doxycycline and trimethoprim-sulfamethoxazole (cotrimoxazole) are bacteriostatic rather than bactericidal in their mechanisms of action.[17]

S. aureus is well known to be a virulent and invasive pathogen. It produces a variety of pyrogenic toxins and superantigens which contribute to its overall virulence.[18] The presence of the Panton-Valentine leukocidin may predispose to invasive skin and soft tissue infections, and also necrotizing pneumonias and other necrotizing infectious localizations. MRSA infection often has its origin from a localized skin infection, with subsequent contiguous or hematogenous spread to lungs, heart (endocarditis), central nervous system (CNS), and sometimes bones and joints and other organs and sites.[19] The prolonged duration of treatment with vancomycin or teicoplanin for severe infections, like endocarditis and osteomyelitis, may lead to more frequent and severe adverse effects (especially nephropathy, serum electrolyte imbalance, and myelotoxicity). While VISA/GISA and VRSA infections have only rarely been reported, clinical hetero-resistant populations of VISA (with strains showing MIC values > 4-16 mcg/mL) have been isolated following prolonged administration of glycopeptides. Moreover, pharmacodynamics of vancomycin may have led to unappreciated under dosing of vancomycin, therefore predisposing to microbial resistance.[20] Coagulase-negative Staphylococci have the capability to produce a glycocalyx enabling them to attach to prosthetic materials.[21] Biofilm formation on the surfaces of medical devices (i.e. prosthetic devices, central vascular catheters), provides a protected environment for coagulase-negative Staphylococci; this biofilm formation impedes antibiotic penetration and reduces target site formation.[21,22] As expected, catheter-related blood stream infections, CNS ventricular shunt infections, prosthetic joint infections, and prosthetic valve endocarditis are commonly caused by coagulase-negative Staphylococci.[23]

The large majority of these microorganisms usually are or become resistant to methicillin. Intermediate resistance to vancomycin was first reported among coagulase-negative Staphylococci several years before it occurred among *S. aureus* strains. Unlike *S. aureus*, infections by coagulase-negative Staphylococci on prosthetic hardware tend to be insidious and more chronic. Therapy often requires a combined medical- surgical approach with removal of the infected device and prolonged duration (usually exceeding four weeks) of antibiotic therapy thereafter.

Vancomycin-resistant Enterococci (VRE) are primarily associated with healthcare institutional acquisition in patients with co-morbid conditions. Since their peak incidence around the year 2000, several new antibiotics with excellent activity against VRE have been introduced into clinical practice in the meantime.

On the other hand, *S. pneumoniae* is the most frequent cause of community acquired pneumonia (CAP). It accounts for at least one third of patients with CAP. The crude incidence of this common pathogen rises to greater than 50%, if respiratory culture with Gram stains and urinary antigen for *S .pneumoniae* are systematically performed. Associated bacteremia occurs in 20% of pneumococcal pneumonias and mortality is notably higher than for other respiratory pathogen. *In vitro* resistance of *S. pneumoniae* to penicillin as currently defined by Clinical Laboratory Standards Institute (CLSI) criteria, does not necessarily correlate with clinical failure. Specifically, penicillins have been favourably efficacious for pneumonia caused by penicillin-resistant pneumococci.[24,25] These resistant isolates are often also resistant to macrolides, and *in vitro* resistance to macrolide does appear to correlate with clinical outcome.[26,27]

In adult patients, *S. pneumoniae* also represents the most common cause of meningitis. Empiric therapy for meningitis with ceftriaxone and vancomycin pending antibiotic susceptibility testing is often employed. Data from a large scale observational study of pneumococcal meningitis suggests that combination therapy may be superior to monotherapy .[28]

Groups A Streptococci (whose leading organism is *Streptococcus pyogenes*), as well as other beta-hemolytic Streptococci, are often associated with life-threatening infections, especially involving the skin and soft tissues. Group B, C, F, and G beta-hemolytic Streptococci can also cause invasive infection and becteremia. *Streptococcus agalactiae* (belonging to group B Streptococci), is a common cause of neonatal sepsis. Fortunately, susceptibility to penicillin remains stable for the majority of the above-mentioned Streptococci.

EPIDEMIOLOGICAL EXPERIENCE AT A MAJOR TERTIARY CARE HOSPITAL IN NORTHERN ITALY

A prospective, microbiological surveillance study is ongoing for a decade at our academic Hospital (S. Orsola-Malpighi Hospital, Bologna, Italy), in order to check the epidemiological-clinical evolution of bacterial and fungal infections occurring among inpatients. All microorganisms isolated and identified from sterile sites (i.e. blood cultures, protected bronchoalveolar lavage, urine culture, and so on), are systematically tested for *in vitro* susceptibility against a consistent panel of antimicrobial compounds, and data are reported quarterly (A. Nanetti and S. Ambretti, unpublished data). Each bacterial isolate cultured from a single patient within one month is counted only once.

Some data regarding *in vitro* sensitivity rates of *Staphylococcus aureus* and Enterococci from the year 2005 to the first nine months of the year 2008 are reported in Table 1.

With regard to *S. aureus*, we underline a progressive reduction of methicillin resistance rate (from 56.8% of strains in the year 2005 up to 44.7% of overall tested strains in the year 2008), while we confirm a maintained 100% susceptibility to all available glycopeptides. Of major interest, the introduction of novel guidelines for a correct antimicrobial use in medicine and surgery seemed to lead to an apparently progressive reduction of the frequency of antibiotic-resistant strains, as demonstrated by an increased mean *in vitro* susceptibility rate against almost all tested compounds demonstrated in the year 2008, *versus* years 2005-2007, together with an apparent progressive trend toward reduced resistances during the examined temporal span (years 2005 to 2008). Furthermore, elevated sensitivity rates are also found for a number of "older" molecules, like cotrimoxazole (87.9% to 98.2%), chloramphenicol (83.5% to 88.6%), followed by rifampicin (60.2% to 80.4%), clindamycin

Table 1. Microbiological figures from patients hospitalized at our tertiary-care hospital (S. Orsola-Malpighi Hospital, Bologna, Italy), year 2005-2008

In vitro antimicrobial susceptibility of Staphylococcus aureus strains isolated from inpatients (years 2005-2008)

Antibiotic susceptibility (190 strains)	**Year 2005 (167 strains)**	**Year 2006 (131 strains)**	**Year 2007 (Jan. to Sep.) (103 strains)**	**Year 2008**
Penicillin	7.9	7.8	9.9	7.8
Amoxicillin-clavulanate	43.2	48.5	48.9	55.3
Cefotaxime/Ceftriaxone	42.9	48.5	48.9	55.3
Methicillin/Oxacillin	43.2	48.5	49.6	55.3
Erithromycin	34.2	48.5	51.9	55.3
Clindamycin	34.9	48.5	51.9	54.4
Chloramphenicol	84.7	88.6	87.8	83.5
Rifampicin	60.2	64.0	62.1	80.4
Cotrimoxazole	87.8	98.2	93.1	95.1
Gentamicin	31.1	41.0	43.5	49.5
Vancomycin/Teicoplanin	100.0	100.0	100.0	100.0

***In vitro* antimicrobial susceptibility of Enterococci isolated from inpatients (years 2005-2008)**

Antibiotic susceptibility	Year 2005 (206 strains)	Year 2006 (151 strains)	Year 2007 (155 strains)	Year 2008 (Jan. to Sep.) (108 strains)
Penicillin	50.0	49.0	51.6	50.9
Ampicillin	50.0	49.0	52.3	51.9
Tetracyclin	46.6	45.0	38.7	38.0
Vancomycin/Teicoplanin	98.1	95.4	94.8	96.3
Linezolid	100,0	100,0	100,0	100,0
Daptomycin	N/A	N/A	N/A	100.0
Quinupristin/Dalfopristin	100,0	100,0	100,0	100,0

(34.9% to 54.4%), and erythromycin (34.2% to 55.3%). These last compounds, which are largely available and do not imply increased costs of administration, are expected to be clinically effective alone and/or in combination with anti-Gram-positive agents (Table 1).

When examining the temporal trend of isolation of Enterococci (as a group) in the same time period (year 2005, up to September 2008), we notice a full sensitivity to novel compounds (i.e. linezolid, daptomycin, and quinupristin/dalfopristin), and a maintained *in vitro* effectiveness of glycopeptides (94.8% to 98.1%). Vancomycin-resistant Enterococci (also called VRE) were isolated infrequently: only 9 cases in the year 2005, 6 in the year 2006, 8 in the year 2007, and only three cases in the first 9 months of the year 2009 (A. Nanetti and S. Ambretti, unpublished data). Also in the case of Enterococci, a number of "older" compounds still retain an effective activity against Enterococci, as demonstrated by susceptibility rates of penicillin (49.0% to 51.6%), ampicillin (49.0% to 52.3%), and tetracyclines (38.0% to 46.6%). Also in this case, these compounds may act favourably or may be a part of a combination regimen, after *in vitro* sensitivity assays (Table 1).

NOVEL ANTIBACTERIAL AGENTS WITH ENHANCED ACTIVITY AGAINST RESISTANT GRAM-POSITIVE COCCI

The following antibacterial agents have been approved during the last five years: quinupristin/dalfopristin,[29-32] linezolid,[33,34] daptomycin,[35-37] and tigecycline.[38,39] Novel lipoglycopeptide agents under study include dalbavancin,[40] telavancin, and oritavancin.[41] Even novel cephalosporins (i.e. cefbiprole), and fluroquinolones (i.e. garenofloxacin) with enhanced activity against MRSA are in the pipeline. Some features of these novel antimicrobial molecule are summarized in Table 2 (microbiological spectrum, clinical indication, adverse events), and in Table 3 (selected pharmacological features).

Quinupristin/Dalfopristin

The so-called streptogramin antibiotic, quinupristin/dalfopristin, is a combination of two semisynthetic pristinamycin derivatives, which are represented by quinupristin and dalfopristin, in a 30:70 ratio. Resistance to quinupristin/dalfopristin can occur by several mechanisms increasing enzymatic modification, active transport of specific efflux

Table 2. Novel antimicrobial agents for the management of resistant gram-positive infections. Microbiological, clinical, and therapeuticfeatures as of the end of 2008. [In vitro antimicrobial susceptibility of staphylococcus aureus strains isolated from inpatients (years 2005-2008)]

Drug	Class	Microbiologically effective on				Adverse events	Clinical indications		
	MRSA	MRSE	PRSP	VRE			Blood stream	Skin-soft tissue	Hospital-acquired pneumonia
Vancomycin	Glycopeptide	+	+	+	Not VISA-VRSA	Nephro- and ototoxicity Red man syndrome	+	+	+
Teicoplanin	Glycopeptide	+	+	+	Not Van-A	N/D	+	+	-
Quinupristin/ Dalfopristin	Streptogramin	+	+	+	E. faecium	Hepatic, phlebitis Artho-myalgias	+ +	+ +	- -
Linezolid	Oxazolidinone	+	+	+	+	Neuropathy, myelotixicity, serotonin syndrome	+	+	+
Daptomycin	Lipopeptide	+	+	+	+	Arthro-myalgias, CPK rise	+	+	-
Tigecycline	Glycopeptide	+	+	+	+	Nausea, diarrhea		+	-
Dalbavancin	Glycopeptide	+	+	+	Not VAN-A	Gastrointestinal, hypokaleamia	+	+	-
Oritavancin - -	Glycopeptide - -	+	+	+	+	N/D	-	+	-
Telavancin	Lipoglycopeptide	+	+	+	+	Altered taste, CNS, phlebitis[7]	-	+	--

Table 3. Novel Antimicrobial Agents for Management of Resistant Gram-positive Infections. Selected Pharmacogical Features Updated at the End of 2008

Drug	Class	Pharmacodynamics binding (%)	Protein route	Elimination adjustment	Dosage	
					Renal	Hepatic
Vancomycin	Glycopeptide	AUC/MIC	10-55	Renal	+	-
Teicoplanin	Glycopeptide	AUC/MIC	90	Renal	+	-
Quinupristin/ Dalfopristin	Streptogramin	AUC/MIC	N/A	Hepatic/feces	N/A	+
Linezolid	Oxazolidinone	AUC/MIC	31	Hepatic	N/A	N/A
Daptomycin	Lipopeptide	AUC/MIC	92	Renal	+	N/A
Tigecycline	Glycopeptide	Time above MIC	68	Biliary	N/A	+
Dalbavancin	Glycopeptide	AUC/MIC	>95	Renal	+	N/A
Oritavancin	Glycopeptide	AUC/MIC	N/A	Renal	Renal	N/A
Telavancin	Lipoglycopep-	AUC/MIC	N/A	Renal	+	-

pumps mediated by an adenosine triphosphate-binding protein, and alteration of the target site. Resistance is rare for Streptococci and *Enterococcus faecium*.[42] This streptogramin combination acts synergistically to inhibit bacterial protein synthesis at the ribosome level. Quinupristin/dalfopristin is therefore active against *Staphylococcus aureus* (including MRSA strains), *Streptococcus pneumoniae*, and Gram-positive anaerobes such as *Clostridium* spp., *Peptococcus* spp., and *Peptostreptococcus* spp. It is effective against vancomycin-sensitive as well as vancomycin-resistant *Enterococcus faecium* (VREF), but has little *in vitro* activity against *Enterococcus faecalis*, so it cannot be recommended until final speciation of Enterococcal organisms is concluded. Dalfopristin/quinipristin association inhibits cytochrome P450 3A4, and can inhibit agents metabolized through this pathway. Dosage adjustments may be needed in patients with hepatic dysfunction. Renal function has minimal impact on the agent's pharmacokinetics. A post-antibiotic effect is observed in 4-5 hours at 4X MIC for Staphylococci, 7-9 hours for Streptococci, and only 4 hours for Enterococci.[43]

The registered clinical indications for quinupristin/dalfopristin use include intra-abdominal infections, bacteremia, urinary tract infection and skin and soft tissue infections in which Enterococci may play a relevant pathogenic role. Overall clinical success rate for patients with vancomycin-resistant *E. faecium* (VREF) proved to be 74%, while overall clinical and bacteriological success rate was 66%.[44] Patients with bacteremia, those on mechanical ventilation, and those undergoing surgery had a worse outcome as might be expected.[44] The most common and notable adverse events were arthralgias and myalgias, as well as vasculitis. In a comparative clinical trial of therapy for Gram-positive skin and soft tissue infections, *S. aureus* was the most frequent pathogen isolated. The clinical success rate of quinupristin/dalfopristin was comparable (68%) to the comparator agents (71%) (cefazolin, oxacillin or vancomycin).[45] A higher incidence of drug-related adverse events occurred with quinopristin/dalfopristin as compared to other agents.[46] For those patients receiving comparator agents, the most common reason for discontinuation was treatment failure (12%).[46] Furthermore, quinupristin/dalfopristin was compared to vancomycin in patients with hospital-acquired pneumonia.[47] Successful outcomes were similar at 56% for quinupristin/dalfopristin and 58% for vancomycin. The bacteriologic success rate was identical for both antibiotic groups, at around 54% of treated cases. Quinupristin/dalfopristin has been also used to treat patients infected by *S. aureus* intolerant to or failing standard therapies.[48]

Ninety patients were treated for an average of 28 days with a 71% clinical outcome of cure or improvement and bacteriologic outcome of eradication or presumed eradication. Infections included bone and joint, skin and soft tissue, bacteremia, endocarditis, and respiratory tract involvement. Adverse events included mainly arthralgias (11%), myalgias (9%), and nausea (9%). However, in patients with hepatic dysfunction or liver transplantation and concurrent receipt of immunosuppressive chemotherapy, the incidence of arthralgias approached 50% of treated subjects.[49,50]

Linezolid

Linezolid is an oxazolidinone antibiotic with activity against Gram-positive pathogens including VRE, MRSA, and VISA. The unique mechanism of action of linezolid involves the inhibition of bacterial protein synthesis through binding to the domain V regions of the 23 Sr RNA gene 46. Resistance to linezolid requires mutations of multiple gene copies, and seems an infrequent phenomenon. Linezolid is 100% bioavailable when given by either oral or intravenous route. Maximal plasma levels are achieved within 1-2 hours after oral dosing. Protein binding is only around 30% with free distribution to well-perfused tissues. The drug does not require dosage alteration in the presence of renal failure, and no interaction exists for cytochrome P450 enzymes (and drugs metabolized through this last pathway). Linezolid and its two metabolites are decreased with hemodialysis, therefore dosing should occur post-dialysis.[51]

Linezolid is currently approved for skin and soft tissue infections and pneumonia due to susceptible pathogens.[52] In two controlled trials of hospital-acquired pneumonia, a trend was seen for linezolid superiority over vancomycin.[53,54] There is little data (mainly based on observational studies), on the utility of linezolid for either bacteremia,[55] or osteomyelitis.[56,57]

Based on a rabbit model, linezolid does not have sufficient CSF penetration and should not be recommended for pneumococcal meningitis.[33] However, CNS penetration appears adequate to treat CSF shunt infections and brain abscesses, too.

The myelotoxicity (especially the thrombocytopenia), is the most common serious adverse event caused by linezolid;[59] it can be ameliorated or prevented by co-administration of pyridoxine (Vitamin B6).[60-63] Both peripheral and optic neuropathy have been reported with prolonged use greater than four consecutive weeks.[64,65] Lactic acidosis has also been reported and is not associated with duration of administration.[65,66] Interaction exists between linezolid and serotonin-reuptake inhibitors (antidepressants drugs). In these last cases, a minority of patients might develop the so-called serotonin syndrome (fever, agitation with mental status changes and tremors). Due to its weak activity as a monoamine oxidase-inhibitor, linezolid should not be used concomitantly with agents, such as tramadol, pethidne, duloxetine, venlafaxine, milnacipran, sibutramine, chlorpeniramine, brompheniramine, cyproheptadine, citalopram, and paroxetine.[65-67] Drug metabolites may accumulate in the event of severe renal failure.

Daptomycin

Daptomycin is the first in a new class of antimicrobial agents: a lipopeptide antibiotic with activity against *S. aureus* (including methicillin-resistant strains), beta-hemolytic Groups A, B, C, and G Streptococci, and Enterococci, including ampicillin- and vancomycin-resistant strains. Both vancomycin-resistant *Staphylococcus aureus* and vancomycin-resistant Enterococci are susceptible to daptomycin. The mechanism of action of daptomycin is unique as the molecule causes a calcium ion dependent disruption of bacterial cell membrane potential resulting in an efflux of potassium, which inhibits RNA, DNA, and protein synthesis. Rare instances of resistance have occurred in clinical trials, although the mechanism of resistance has not yet been clearly identified to date. Daptomycin was shown to have a rapidly bactericidal effect *in vitro* against Gram-positive drug-resistant pathogens. Its activity is concentration-dependent and once daily dosing is associated with significant post-antibiotic effect.

Daptomycin is highly protein bound (around 92%), with a terminal half-life of 8 hours, which allows for once daily dosing. Post-antibiotic effect proves to be dose dependent, and is reduced in the presence of albumin (i.e. exudates). The drug volume of distribution is low (0.1L/kg) and the Cmax (54.6mcg/mL) is unchanged at steady state, and is achieved by day three of administration in humans. Cmax concentrations occur at the end of a 30-minutes infusion. Dosage needs to be reduced and dosing interval extended to every 48 hours in patients with reduced creatinine clearance <30 mL/min; the same occurs for patients on either hemodialysis or peritoneal dialysis; the daptomycin dose is in these patients becomes 4 mg/kg every 48 hours. Daptomycin should be administered after hemodialysis as approximately 15% is cleared per 4-hour hemodialysis session. On the other hand, no dose adjustments for hepatic dysfunction are required.

In early clinical trials conducted in the years 1980's-1990's, daptomycin was given in divided daily doses of 2 mg/kg every 12 hours for skin and soft tissue infection and 3 mg/kg every 12 hours for bacteremia, achieving good clinical and bacteriological outcomes. However, rise in serum creatine phosphokinase (CPK), with myalgias, and muscle weakness led to initial abandonment of this promising antibiotic. However, myopathy was reversible upon drug cessation. With the advent of MRSA infections, daptomycin has been re-examined and resurrected, and its dosage has been increased to 4 mg/kg daily for skin and soft-tissue infection,[68] and up to 6 mg/kg daily for bacteremia and endocarditis.[69] Both indications have been approved by the United States FDA. Otherwise, daptomycin is not approved for the treatment of bacterial pneumonia; its efficacy is significantly compromised by its interaction with pulmonary surfactant.[70] Significant drug-drug interaction occurs with the statins, and patients receiving HMG-CoA reductase inhibitors; these drugs should be suspended and avoided while the patient is undergoing a daptomycin course.

Tigecycline

Tigecycline is a novel glycylcycline molecule, which is a derivative of the tetracycline minocycline. Resistance to the tetracycline class is classically mediated by ribosomal protection mechanisms or by active efflux. Tigecycline has more potent activity against tetracycline-resistant organisms, and maintains a broad antibacterial spectrum against Gran-positive and also Gram-negative pathogens. Tigecycline binds more avidly to the ribosome and either does not induce efflux proteins or is not readily exported by efflux proteins.[38] Resistant clinical isolates were associated with up-regulation of chromosomally mediated efflux pumps. Unlike original tetracyclines, tigecycline has a large volume of distribution (above 10 L/kg), the protein binding is approximately 68%, the terminal half-life of elimination is 36 hours, and less than 15% of the native drug is excreted unchanged in the urine.

Clinical trials have been conducted in patients with complicated skin and soft tissue infections and intra-abdominal infections for which the drug gained its United States FDA approval.

Based on *in vitro* susceptibility data, tigecycline has a broad spectrum of activity against both Gram-positive cocci (including methicillin-resistant Staphylococci or MRSA, penicillin-resistant *Streptococcus pneumoniae*, beta-hemolytic group A and group B Streptococci, Enterococci (vancomycin-susceptible ones), and *Listeria monocytogenes*. Unlike other new agents for Gram-positive cocci, tigecycline also has extensive activity against Gram-negative pathogens, including *Haemophilus influenzae*, *Neisseria* spp,[11] Enterobacteriaceae, and non-lactose fermenters other than *Pseudomonas aeruginosa*. The MIC_{90} values for *Proteus* spp., *Providentia* spp., and *Burkholderia cepacia* is 8 mcg/mL, limiting its utility in infections caused by these afore mentioned pathogens.

Tigecycline needs no reduction in renal impairment and it is not dialyzable. Patients with severe hepatic dysfunction (Child-Pugh stage C liver disease) should receive a lower dosage. Tigecycline activity is dependent on the time above the MIC, and the drug concentrations should be above the MIC values for at least 50% of the dosing interval.

The expected adverse effects of tigeciclyne are primarily gastrointestinal in origin, with nausea, vomiting, diarrhea, and heartburn as the most frequent. As with all tetracyclines, tigecycline is contraindicated for pregnant females and for children less than 8 years of age.[71] Drug interactions of tigecycline with either digoxin or warfarin do not alter the effect of either drug. Tigecycline does not inhibit metabolism mediated by the cytochrome P450 isoforms IA2, 2C8, 2C9, 2C19, 2D6 and 3A4, so that no drug-drug interaction is expected with drugs metabolized by these cytochrome isoforms.

Dalbavancin

Dalbavancin is a true second-generation lipoglycopeptide. Its unique pharmacokinetic profile allows once weekly dosing. It is not active against VRE, but has an excellent activity against MRSA, *S. pyogenes* and *S. pneumoniae* as well as vancomycin-susceptible Enterococci. It is bactericidal and synergistic with ampicillin against Van-A type Enterococci. The mechanism of action is the inhibition of the cell wall peptidoglycan cross-linking.

The daily dosage is 1000 mg IV once, followed by 500 mg IM 7 days later; the terminal half-life of dalbavancin is 9-12 days in humans due to protein binding greater than 95%. Animal models of infection show excellent activity against MRSA or GISA endocarditis, penicillin-resistant *Streptococcus pneumoniae*[12] pneumonia or MRSA pouch infection, and septicemia due to Staphylococci, Streptococci or Enterococci. This antibiotic has been evaluated for catheter-related bacteremia[72] and skin and soft tissue infections.[73] Dalbavancin was effective and well tolerated in adult patients with catheter-related bacteremia caused by coagulase-negative Staphylococci, MSSA and MRSA in a comparative trial with vancomycin. In skin and soft tissue infections, a 92-94% microbiological and clinical response respectively was found in an open label phase 2 comparative dosing trial.[73] Clinical success at follow-up visits for the two dose dalbavancin group was 80% for MRSA *versus* 50% for comparator therapy (which included beta-lactams, clindamycin, vancomycin and linezolid, respectively).

Oritavancin

Oritavancin is another derivative of vancomycin: it is a chloroeremomycin with the substitution of vancosamine by epi-vancosamine. It has a similar spectrum of activity to vancomycin but with consistently lower MIC values (<1 mg/L). No resistance to oritavancin has been observed among *S. aureus* strains including VISA strains, but VAN-A and VAN-B strains of Enterococci with reduced susceptibility to oritavancin have been obtained *in vitro*. The known mechanisms of resistance of oritavancin are: 1) complete elimination of D-Ala-entry precursors; 2) mutations in the VAN Sb sensor of VAN B cluster; or 3) the expression of Van Z (the precise function of which is still unknown).

Oritavancin shows rapid concentration bactericidal-dependent activity with a concentration-dependent post-antibiotic effect exerted against both VRE and MRSA. Oritavancin activity is negatively affected by large inoculum and its activity *versus* VRE was slightly reduced in stationary phase or in acidic foci of infection. In animal models, its efficacy has been demonstrated for experimental MRSA endocarditis and *S. pneumoniae* meningitis.[74,75] In a reliable endocarditis model, the addition of gentamicin proved to be synergistic and able to prevent the emergence of resistant mutants. With regard to skin and soft tissue infections, oritavancin proved to be at least equivalent to vancomycin, for both clinical and bacteriological cure (about 78% cure rate).[76]

Telavancin

Telavancin is a rapidly bactericidal lipoglycopeptide analogue of vancomycin. The mechanism of action of this molecule is by inhibition of peptidoglycan chain formation through blockage of both the transpeptidation and transglycosylation steps; and by a direct effect on the bacterial membrane dissipating membrane potential and effecting changes in cellular permeability.

The *in vitro* activity of telavancin demonstrates enhanced activity against MRSA, penicillin-resistant *S. pneumoniae*, GISA and Van-A type Enterococci. Telavancin achieves a higher volume of distribution into tissues and a prolonged half-life.[77] A high level of protein binding (93%) occurs in human plasma and repetitive dosing does not lead to accumulation. The terminal half-life is 7-9 hours at doses above 5 mg/kg.[78] Telavancin exhibit time-dependent killing activity.[79]

Telavancin and its comparators of vancomycin or beta-lactam agent have been compared in a phase 2 clinical trial for skin and skin-structure infections. Clinical cure rates were similar at 92% for telavancin *versus* 96% for comparator agents. Microbiologic rates of cure were noted to be 93% in the telavancin group and 95% among the comparator group.[80] For complicated skin and soft tissue infections, clinical cure rates were at 96% for telavancin and 90% for comparator agents. Microbiologic eradication was better with telavancin (92%) *versus* comparator agents (78%, p = 0.07).[80] Telavancin is currently under assessment in phase 3 trials of hospital-acquired pneumonia.

Adverse events associated with telavancin among evaluated patients included vomiting, paresthesias, and dyspnea. Laboratory abnormalities included microalbuminemia and a decreased platelet count.[81]

CLINICAL INDICATIONS OF NOVEL ANTIBIOTICS WITH EXPANDED SPECTRUM AGAINST RESISTANT GRAM-POSITIVE COCCI

Skin and soft-tissue infections

Skin and soft-tissue infections caused by Gram-positive cocci range from a simple cellulitis to life-threatening necrotizing fasciitis. All of the newer agents have been studied for such infections and have been found to be efficacious (Table 2). Most of the patients in these studies had less severe infections than necrotizing fasciitis as that infection requires a surgical approach as well as antibiotic therapy. All five FDA-approved agents, i.e. quinupristin/dalfopristin, linezolid, daptomycin, tigecycline, and vancomycin are appropriate choices for an effective treatment of Gram-positive pathogens. Only tigecycline has activity against Gram-negative bacilli pathogens. So, tigecycline may have a major role for diabetic foot infections and infected decubitus ulcers which may be co-infected by anaerobic bacteria and aerobic Gram-negative bacilli, in addition to Gram-positive cocci.

Bone and joint infections

With regard to osteomyelitis and joint infections, Gram-positive cocci largely predominate over other microbial pathogens. *S. aureus*, and both MSSA and MRSA, as well as coagulase-negative Staphylococci account for over 50% of recovered pathogens. Unfortunately, only few studies have prospectively investigated the above-mentioned newer antibiotics in these infections.[56,57] Aneziokoro *et al*. evaluated 20 patients who received linezolid for osteomyelitis for 6 weeks or more in a retrospective non-comparative study.[82] Fifty-five percent of cases (11 patients) achieved a cure with follow-up periods ranging from 6 to 49 months (median of 36 months). Prospective comparative studies of efficacy in bone and joint infections have not been reported to date. In two retrospective studies, 22 patients with osteomyelitis and three subjects with septic joint infections were treated with daptomycin.[83,84] MRSA was the predominant pathogen in over 75% of patients. Daptomycin was used as salvage therapy, and its usual dose was 6 mg/kg/day. Clinical success rate was about 90%; follow up periods were one year or less. Limited data has been published with respect to bone and joint infections for dalbavancin, tigecycline or quinupristin/dalfopristin in humans. In a rabbit model of MRSA osteomyelitis, the combination of rifampin and tigecycline was compared to vancomycin with or without rifampicin, tigecycline alone, and vancomycin alone.[85] All regimens were effective (in about 90% of episodes). Untreated rabbits had spontaneous cure in 26% of cases (4/15). Tigecycline concentrations are higher in infected bone than in non-infected bone. A rabbit model of quinupristin/dalfopristin prosthetic joint infection with MRSA was compared to vancomycin with or without rifampicin, showing an equivalent outcome.[86]

Pneumonia and lower respiratory tract infections

Pneumonia due to Gram-positive cocci is common. In the community, infection is usually due to *S. pneumoniae* and occasionally *S. aureus*. Hospital-acquired pneumonia (HAP) is often caused by MRSA organisms. Linezolid was comparable to vancomycin in the therapy of MRSA-associated VAP, although a trend was seen for linezolid superiority.[53,54] Daptomycin is not indicated for pneumonia due to its interaction with surfactant,[70] while tigecycline is undergoing clinical evaluation. Quinupristin/dalfopristin has been compared to vancomycin for hospital-acquired pneumonia.[47] One hundred and seventy one patients had similar clinical response rates of about 57% respectively. Drug discontinuation adverse events occurred more frequently in the quinupristin/dalfopristin group (15%), as compared to vancomycin. Only two isolated of the 87 overall strains were shown to have decreased susceptibility to quinupristin/dalfopristin during and after treatment.

Intra-abdominal infections

Of the newer antibiotics, only tigecycline has been approved for intra-abdominal infections. As mentioned, tigecycline's broader spectrum of activity includes Gram-negative bacilli and anaerobic bacilli. Linezolid, daptomycin, and quinupristin/dalfopristin can be used in combination with antibiotics with Gram-negative spectrum of activity such as aztreonam, and especially carbapenems, fluoroquinolones, and aminoglycosides. Of concern, quinupristin/dalfopristin has no activity against E. faecalis.

Bacteremia and endocarditis

Daptomycin and quinipristin/dalfopristin have been approved by the United States FDA organisms for the treatment of Gram-positive bacteremia. In addition, daptomycin has been approved for use in *S. aureus* right-sided endocarditis.[87] Dalbavancin, linezolid, tigecycline and oritavancin have not yet been approved for bacteremia due to Gram-positive cocci. Linezolid has been evaluated for Gram-positive bacteria.[55,88,89] Among 108 bacteremic patients receiving linezolid, eradication was seen in 91% and clinical cure was seen in 94% of the episodes.[55] On the other hand, linezolid is still not approved for catheter-related becteremia and endocarditis. A randomized study of 726 patients with catheter-related bacteremia received linezolid or vancomycin; an excess number of deaths were seen for patients receiving linezolid due mainly to Gram-negative rods implicated in these infections.[90] Based on 23 case reports and three case series, a total of 63% (21/33) of patients with endocarditis were successfully cured after linezolid administration.[91] MRSA and vancomycin-intermediate *S. aureus* were the most commonly isolated cocci (24.2% and 30.3% of cases, respectively). Five cases were successfully treated with linezolid monotherapy.

POTENTIAL SYNERGISTIC INTERACTIONS OF NEWER ANTIBIOTICS: IN VITRO STUDIES

In vitro interaction between the new anti-staphylococcal antibiotics were virtually always indifferent, therefore leading to a possible additive effect, although a few experiments showed possible (Table 4).[89,92-95,98-107] For instance, a synergistic interaction was found for quinupristin/dalfopristin and vancomycin in two independent studies.[92,93]

Table 4. Some experimental studies conducted in vitro or on animal models, regarding possible interactions between the different antimicrobial agents effective on Gram-positive Cocci[89,92-95,98-107]

Reference quotation	Combination	Pathogens	Interaction
97	Daptomycin + vancomycin	GISA	Additive
97	Daptomycin + gentamicin	GISA	Additive
93	Daptomycin + gentamicin	MSSA/MRSA	Enhanced time-kill
98	Daptomycin + gentamicin	MSSA/MRSA	Increased killing
99	Daptomycin + rifampicin	MRSA	Additive
100	Daptomycin + gentamicin + rifampicin	MRSA	Additive
97	Linezolid + vancomycin	GISA	Additive
94	Linezolid + vancomycin	MSSA/MRSA	Antagonistic
89, 95	Linezolid + vancomycin	MRSA	Indifferent
101	Linezolid + vancomycin	MSSA/MRSA/MRSE	Increased killing
94, 98	Linezolid + gentamicin	MSSA/MRSA	Indifferent
95	Linezolid + gentamicin	MRSA	Antagonistic
94	Linezolid + rifampicin	MSSA/MRSA	Indifferent
95	Linezolid + rifampicin	MSSA/MRSA	Synergistic
102	Linezolid + rifampicin	MSSA	Indifferent
101	Linezolid + quinupristin/dalfopristin	MRSA	Increased killing
97	Quinupristin/dalfopristin + vancomycin	GISA	Additive-Synergistic
103	Quinupristin/dalfopristin + vancomycin	MSSA/MRSA	Additive
101	Quinupristin/dalfopristin + vancomycin	MRSA	Increased killing
92	Quinupristin/dalfopristin + vancomycin	MSSA/MRSA	Synergistic
97	Quinupristin/dalfopristin + gentamicin	GISA	Indifferent
104	Quinupristin/dalfopristin + rifampicin	MSSA	Increased killing
105	Quinupristin/dalfopristin + rifampicin	MRSA	Synergistic
106	Tigecycline + vancomycin	MRSA	Indifferent
107	Tigecycline + gentamicin	MRSA/GISA	Increased killing
106	Tigecycline + rifampicin	MRSA	Indifferent

On the other hand, antagonistic interactions were demonstrated for the combination of linezolid plus vancomycin,[94] and linezolid plus gentamicin.[95] It should be emphasized that *in vitro* interaction may not translate into clinical efficacy. Quinupristin/dafloplistin in combination with vancomycin appeared to be favourable for the management of MRSA infections responding poorly to vancomycin.[96] However, we have to specify that the MRSA isolates were of a specific genotype, accessory gene regulator (agr), which has been linked to vancomycin treatment failure.[96] Nevertheless, such information may be useful if innovative combination therapy needs to be administered to severely ill patients with invasive *S. aureus* infection unresponsive to monotherapy.

Controlled clinical trials using combinations including these new agents are indicated for patients with severe, life-threatening infections caused by gram-positive cocci, and randomized trials are strongly warranted in this somewhat unexplored field.

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