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REVIEW

New antimicrobial agents as therapy for resistant gram-positive cocci

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Abstract Vancomycin- and methicillin-resistant gram-positive cocci have emerged as an increasingly problematic cause of hospital-acquired infections. We conducted a literature review of newer antibiotics with activity against vancomycin-resistant and methicillin-resistant gram-positive cocci. Quinupristin/dalfopristin, linezolid, daptomycin, and tigecycline have *in vitro* activity for methicillin-resistant staphylococci and are superior to vancomycin for vancomycin-resistant isolates. Dalbavancin, telavancin, and oritavancin are new glycopeptides that have superior pharmacodynamic properties compared to vancomycin. We review the antibacterial spectrum, clinical indications and contraindications, pharmacologic properties, and adverse events associated with each of these agents. Daptomycin has rapid bactericidal activity for *Staphylococcus aureus* and is approved for use in bacteremia and right-sided endocarditis. Linezolid is comparable to vancomycin in patients with methicillin-resistant *S. aureus* (MRSA) pneumonia and has pharmacoeconomic advantages given its oral formulation. Quinupristin/dalfopristin is the drug of choice for vancomycin-resistant *Enterococcus faecium* infections but has no activity against *Enterococcus faecalis*. Tigecycline has activity against both enterococcus species and MRSA; it is also active against *Enterobacteriaceae* and anaerobes which allows for use in intra-abdominal and diabetic foot infections. A review of numerous *in vitro* and animal model studies shows that interaction between these newer agents and other antistaphylococcal agents for *S. aureus* are usually indifferent (additive).

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History of antibiotic resistance among gram-positive cocci

Gram-positive cocci have reemerged as predominant pathogens of human hosts within the past decade. With the introduction of penicillin, infections by *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* became treatable. Within a short period of time, however, *S. aureus* developed resistance to penicillin. Penicillinase-resistant penicillins were successfully introduced with success in the early 1960s. Concomitantly, resistance emerged for the penicillinase-resistant penicillins; methicillin- resistant *S. aureus* (MRSA) became a major hospital-acquired pathogen. Vancomycin was an active agent against MRSA and coagulase-negative staphylococci and was increasingly used.

From the 1990s to the present, however, emergence of resistance to vancomycin also occurred [1–3]. First among these organisms were *Enterococcus faecium* and *Enterococcus faecalis* [4]. Vancomycin-resistant enterococci (VRE) became a major hospital-acquired pathogen. In the past several years, MRSA were also spreading clonally into

the community (CA-MRSA) leading to increased use of vancomycin therapy [5]. In the late 1990s, glycopeptide resistance was reported for a coagulase-negative staphylococcus [6] and then *S. aureus* (vancomycin- intermediate *S. aureus*-VISA or glycopeptide-intermediate *S. aureus*-GISA). The first reported isolation of VISA occurred in Japan in 1997 [7] and more than 100 VISA isolates have since been reported [8]. In 2002, three vancomycin-resistant *S. aureus* (VRSA) from clinical specimens of American patients were found to have high-level resistance to vancomycin [minimal inhibitory concentration (MIC) >32 ug/ml] [9]. Although a few more cases of VRSA have since been described [10], fortunately, these isolates have not yet become widespread.

Infections due to gram-positive cocci

Reemergence of gram-positive cocci has been well established in hospital-acquired infections, but community-acquired infections due to MRSA have become increasingly problematic [11–13]. Foreign body infections and bacteremia caused by coagulase-negative staphylococci have also increased [14]. As a result, vancomycin usage has increased. Although most *S. aureus* remain susceptible *in vitro* to vancomycin, its efficacy against methicillin-sensitive *S. aureus* (MSSA) is inferior to that of penicillinase-resistant penicillins [15, 16].

MRSA is a multidrug-resistant pathogen. Resistance to the macrolides, lincosamides, aminoglycosides, and all beta-lactam agents is also seen with MRSA. Rifampin should not be used as a single agent due to rapid emergence of resistance, while doxycycline and trimethoprim-sulfamethoxazole are bacteriostatic rather than bactericidal [17].

S. aureus is a virulent and invasive pathogen. It produces a variety of pyrogenic toxins and superantigens which contribute to their overall virulence [18]. The presence of the Panton-Valentine leukocidin may predispose to invasive skin and soft tissue infections and necrotizing pneumonias. Infection is often initiated by a localized skin infection with subsequent contiguous or hematogenous spread to lung, heart (endocarditis), CNS, and bones and joints [19]. The prolonged duration of vancomycin therapy for endocarditis and osteomyelitis may lead to adverse effects (especially neutropenia). While VISA/GISA and VRSA infections have only rarely been reported, clinical heteroresistant populations of VISA (MIC >4–16 μg/ml) have been isolated following prolonged duration for vancomycin. Pharmacodynamics of vancomycin may have led to unappreciated underdosing of vancomycin predisposing to 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 provides a protected environment for coagulase-negative staphylococci; the biofilm impedes antibiotic penetration and reduces target site formation [21, 22]. Catheter-related bloodstream infections, central nervous system ventricular shunt infections, prosthetic joint infections, and prosthetic valve endocarditis are commonly caused by coagulase-negative staphylococci [23]. These organisms are usually resistant to methicillin. Intermediate resistance to vancomycin was first reported in coagulase-negative staphylococci several years before it occurred in *S. aureus*. 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 device and prolonged duration (>4 weeks) of antibiotic therapy thereafter.

Since their peak incidence in 2000, several new antibiotics with activity against VRE (vancomycin-resistant enterococci) have been introduced into clinical practice. In the USA, VRE are primarily associated with healthcare institutional acquisition in patients with comorbid conditions, whereas in many European countries, community-acquired colonization with VRE has occurred. The epidemiological differences were due to two primary factors: in Europe, avoparcin, a glycopeptide antibiotic, was used as a growth enhancer in farm animals. Following transfer of the VRE resistance genes to humans via the food chain, avoparcin has been banned from use in Europe. Throughout the USA, clinical usage of vancomycin was excessive; this served to amplify the VRE clones which were in circulation within US hospitals. Inadequate infection control practices further increased the prevalence of VRE in the USA [24–26].

S. pneumoniae is the most frequent cause of community-acquired pneumonia (CAP). It is accounts for at least one third of patients with CAP. The incidence rises to greater than 50% if respiratory culture with gram stains and the test for urinary antigen for *S. pneumoniae* are performed. Associated bacteremia occurs in 20% of pneumococcal pneumonias and mortality is notably higher than for other respiratory pathogens. *In vitro* resistance of *S. pneumoniae* to penicillin, as currently defined by Clinical and Laboratory Standards Institute (CLSI) criteria, does not correlate with clinical failure. Specifically, penicillins have been efficacious for pneumonia caused by penicillin-resistant pneumococci [27, 28]. These resistant isolates are often also resistant to macrolides, and *in vitro* resistance of macrolide does appear to correlate with outcome [29, 30]. In adults, *S. pneumoniae* is 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 suggest that combination therapy may be superior to monotherapy [31].

Group A streptococci (*Streptococcus pyogenes*) as well as other beta-hemolytic streptococci are often associated with life-threatening infections especially of the skin and soft tissue. Group B, C, F, and G beta-hemolytic streptococci can also cause invasive infection and bacteremia. *S. agalactiae* (group B) is a common cause of neonatal sepsis. Fortunately, susceptibility to penicillin remains stable for most streptococci.

Newer antibiotics with enhanced activity against gram-positive cocci

In order of commercial introduction, the following antibacterial agents have been approved: quinupristin/dalfopristin (Synercid®, Monarch Pharmaceuticals, Inc., Bristol, TN, USA) [32–35], linezolid (Zyvox®, ZyvoxID®, Pfizer, Inc., New York, NY, USA) [36, 37], daptomycin (Cubicin®, Cubist Pharmaceuticals, Lexington, MA, USA) [38–40], and tigecycline (Tygacil®, Wyeth Pharmaceuticals, Inc., Madison, NJ, USA) [41, 42]. Glycopeptides under study include dalbavancin (Zeven®, Pfizer, Inc., New York, NY, USA) [43], telavancin (TD-6424, Theravance, South San Francisco, CA, USA), and oritavancin (Targanta Therapeutics, Cambridge, MA, USA) [44].

Quinupristin/dalfopristin (Synercid®, Monarch Pharmaceuticals, Inc.)

The streptogramin antibiotic, quinupristin/dalfopristin is a combination of two semisynthetic pristinamycin derivatives: quinupristin and dalfopristin in 30:70 ratio. Resistance can occur by several mechanisms including increasing enzymatic modification, active transport of efflux mediated by an adenosine triphosphate-binding protein, and alteration of the target site. Resistance is rare for streptococci and *Enterococcus faecium* [45]. Combination acts synergistically to inhibit bacterial protein synthesis at the ribosome level.

Quinupristin/dalfopristin is active against *S. aureus*, including MRSA, *S. 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 *E. faecalis*. The drug 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. The post-antibiotic effect is observed at 4–5 h at 4× MIC versus staphylococci, 7–9 h for streptococci, and only 4 h for enterococci [46].

Clinical indications for quinupristin/dalfopristin include intra-abdominal infections, bacteremia, urinary tract infection, and skin and soft tissue infections in which enterococcus may be a pathogen. The overall clinical success rate for patients with vancomycin-resistant *E. faecium* (VREF) was 74%, while the overall clinical and bacteriological success rate was 66% [47]. Patients with bacteremia, on a mechanical ventilator, and undergoing surgery had a worse outcome as might be expected [47]. The most common and notable adverse events were arthralgias and myalgias.

In a comparative trial of therapy for gram-positive skin and soft tissue infections, *S. aureus* was the most frequent pathogen isolated [48]. The clinical success rate of quinupristin/dalfopristin was comparable (68%) to the comparator agents (71%). A higher incidence of drug-related adverse events occurred with quinupristin/dalfopristin as compared to other agents [49]. For those patients receiving comparator agents, the most common reason for discontinuation was treatment failure (12%) [49]. Quinupristin/dalfopristin was compared to vancomycin in patients with hospital-acquired pneumonia [50]. Successful outcomes were similar at 56% for quinupristin/dalfopristin and 58% for vancomycin. The bacteriologic success rate was identical for both antibiotic groups at 54%.

Quinupristin/dalfopristin has been used to treat patients infected by *S. aureus* intolerant of or failing standard therapies [51]. Ninety patients were treated an average of 28 days with a 71% clinical outcome of cure or improvement and bacteriologic outcome of eradication or presumed eradication. The infections treated included bone and joint, skin and soft tissue, bacteremia, endocarditis, and respiratory tract. Adverse events included arthralgias (11%), myalgias (9%), and nausea (9%). However, in patients with hepatic dysfunction or liver transplantation and receipt of immunosuppressive chemotherapy, the incidence of arthralgias approached 50% [52, 53]

Linezolid (Zyvox®, ZyvoxID®, Pfizer, Inc.)

Linezolid is an oxazolidinone antibiotic with activity against gram-positive pathogens including VRE, MRSA, and VISA. The unique mechanism of action involves inhibition of bacterial protein synthesis through binding to the domain V regions of the 23S rRNA gene [49]. Resistance to linezolid requires mutations of multiple gene copies.

Linezolid is 100% bioavailable when given by either oral or intravenous route. Maximal plasma levels are achieved within 1–2 h after oral dosing. Protein binding is only 31% 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. Linezolid and its two metabolites are decreased with hemodialysis, so dosing should occur postdialysis [54].

Linezolid is currently approved for skin and soft tissue infections and pneumonia due to susceptible pathogens [55]. In two controlled trials of hospital-acquired pneumonia, a trend was seen for linezolid superiority over vancomycin [56, 57]. There are few data on utility of linezolid for either bacteremia [58] or osteomyelitis [59, 60]. Based on a rabbit model, linezolid does not have sufficient CSF penetration and is not recommended for pneumococcal meningitis [36]. However, CNS penetration appears adequate to treat CSF shunt infections [61].

The oral availability of an anti-MRSA agent allows the substitution of linezolid for vancomycin. The tremendous savings in hospitalization costs more than offsets the higher price of linezolid. Adverse effects can be serious. Bone marrow suppression, especially thrombocytopenia, is the most common serious adverse effect [62]; it can be ameliorated or prevented by coadministration of pyridoxine (vitamin B_6) [63–66]. Both peripheral and optic neuropathy have been reported with prolonged use of greater than 28 days [67, 68]. Lactic acidosis has also been reported and is not associated with duration of usage [68, 69]. Interaction exists between linezolid and serotonin reuptake inhibitors. Patients may develop the 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, pethidine, duloxetine, venlafaxine, milnacipran, sibutramine, chlorpheniramine, brompheniramine, cyproheptadine, citalopram, and paroxetine [68, 70]. Metabolites may accumulate in severe renal failure.

Daptomycin (Cubicin®, Cubist Pharmaceuticals)

Daptomycin is a new lipopeptide antibiotic with activity against *S. aureus* (including methicillin-resistant strains), beta-hemolytic groups A, B, C, and G streptococci and enterococci, and ampicillin- and vancomycin-resistant strains. The mechanism of action is unique as daptomycin 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 identified. 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 (PAE). PAE is defined as the transient suppression of bacterial growth after exposure to an antibiotic following removal of the antibiotic by dilution in an *in vitro* assay. In vivo, PAE reflects bactericidal effect after the antibiotic level has decreased below the minimal inhibitory concentration. PAE is expressed in units of time, usually hours.

The drug is highly protein bound (92%) with a $t_{1/2}$ of 8 h allowing for once daily dosing. The post-antibiotic effect was dose dependent and reduced in the presence of albumin. The volume of distribution is low (0.1 l/kg) and C_{max} (54.6 μg/ml) unchanged at steady state is achieved by day 3 of therapy. C_{max} is defined as the highest therapeutic concentration of antibiotic achievable without inducing toxicity to the host. C_{max} occurs at the end of a 30-min infusion. Dosage needs to be reduced and dosing interval extended to every 48 h in patients with reduced creatinine clearance <30 ml/min; and for patients on either hemodialysis or peritoneal dialysis, the dose is 4 mg/kg every 48 h. Daptomycin should be administered after hemodialysis as approximately 15% is cleared per 4-h hemodialysis session. No adjustments for hepatic dysfunction are required.

In early clinical trails in the 1980s–1990s, daptomycin was given in divided daily doses of 2 mg/kg every 12 h for skin and soft tissue infection and 3 mg/kg every 12 h for bacteremia with good clinical and bacteriological outcomes. However, rise in serum creatine phosphokinase with myalgias and muscle weakness led to abandonment of this promising antibiotic. Myopathy was reversible upon cessation of the drug. With the advent of MRSA infections, daptomycin has been resurrected and dosage has been increased to 4 mg/kg daily for skin and soft tissue infection [71] and to 6 mg/kg daily for bacteremia and endocarditis [72]. Both indications are approved by the FDA.

Daptomycin is not approved for the treatment of bacterial pneumonia; its efficacy is compromised by interaction with pulmonary surfactant [73]. Significant drug interaction occurs with the statins and patients receiving HMG-CoA reductase inhibitors; these drugs should be suspended while receiving daptomycin.

Tigecycline (Tygacil®, Wyeth Pharmceuticals, Inc.)

Tigecycline is a glycylcycline which is a derivative of minocycline. Resistance to the tetracycline class is mediated by ribosomal protection mechanisms or by efflux. Tigecycline has more potent activity against tetracycline-resistant organisms. Tigecycline binds more avidly to the ribosome and either does not induce efflux proteins or is not readily exported by efflux proteins [41]. Resistant clinical isolates were associated with upregulation of chromosomally mediated efflux pumps. Unlike other tetracyclines, tigecycline has a large volume of distribution (>10 l/kg), protein binding is approximately 68%, the $t_{1/2}$ is 36 h, and less than 15% 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 has FDA approval.

Based on *in vitro* susceptibility data, tigecycline has a broad spectrum of activity against both gram-positive cocci including methicillin-resistant staphylococci, penicillin-resistant *Streptococcus pneumoniae*, beta-hemolytic group A and group B streptococci, enterococci (vancomycin-susceptible), 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., *Enterobacteriaceae*, and non-lactose fermenters other than *Pseudomonas aeruginosa*. The MIC 90 for *Proteus* spp., *Providencia* spp., and *Burkholderia* is ≥8 μg/ml which limits its utility in infections caused by those pathogens.

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

Adverse effects are primarily gastrointestinal with nausea, vomiting, diarrhea, and heartburn. As with all tetracyclines, tigecycline is contraindicated for pregnant females and for children less than 8 years of age [74]. Drug interactions of tigecycline with either digoxin or warfarin do not alter the effect of either drug. Tigecycline does not inhibit metabolism mediated by cytochrome P450 isoforms: IA2, 2C8, 2C9, 2C19, 2D6, and 3A4.

Dalbavancin (Zeven®, Pfizer, Inc.)

Dalbavancin (B1 397) is a second-generation glycopeptide. Its unique pharmacokinetic profile allows once weekly dosing. It is not active against VRE, but has 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 inhibition of cell wall peptidoglycan cross-linking.

Dosage is 1000 mg IV once followed by 500 mg IV 7 days later; the $t_{1/2}$ is 9–12 days in humans due to protein binding of greater than 95%. Animal models of infection show excellent activity in MRSA or GISA endocarditis, penicillin-resistant *Streptococcus pneumoniae* pneumonia *or* MRSA pouch infection, and septicemia due to staphylococci, streptococci, or enterococci.

This antibiotic has been evaluated for catheter-related bacteremia [75] and skin and soft tissue infections [76]. 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 and 94% microbiologic and clinical response, respectively, was found in an open-label phase 2 comparative dosing trial [76]. Clinical success at follow-up visit for the 2-dose dalbavancin group was 80% for MRSA vs 50% for comparator therapy (which included beta-lactams, clindamycin, vancomycin, and linezolid).

Oritavancin (Targanta Therapeutics)

Oritavancin is obtained by reductive alkylation of chloroeremomycin, a naturally occurring fermentation product of *Amycolatopsis orientalis*, which differs from vancomycin by substitution of the vancosamine of the disaccharide moiety by an epivancosamine. It has a similar spectrum of activity to vancomycin but with consistently lower MICs <1 mg/l. No resistance to oritavancin has been noted among *S. aureus* including VISA strains, but Van A and Van B strains of enterococci with reduced susceptibility to oritavancin have been obtained *in vitro*. The mechanisms of resistance are: (1) complete elimination of D-Ala-entry precursors, (2) mutations in the Van Sb sensor of the Van B cluster, or (3) expression of Van Z, the precise function of which is unknown.

Oritavancin shows rapid, concentration-dependent bactericidal activity with a concentration-dependent post-antibiotic effect against VRE and MRSA. Oritavancin activity is negatively affected by large inoculum and activity vs VRE was slightly reduced in stationary phase or in acidic foci of infection. In animal models, efficacy has been demonstrated for MRSA endocarditis and *S. pneumoniae* meningitis [77, 78]. In the endocarditis model, addition of gentamicin proved to be synergistic and able to prevent emergence of resistant mutants. In skin and soft tissue infections, oritavancin was equivalent to vancomycin for both clinical and bacteriological cure (about 78%) [79].

Telavancin (Theravance, Inc.)

Telavancin is a rapidly bactericidal lipoglycopeptide analog of vancomycin. The mechanism of action 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 prolongation of half-life [80]. A high level of protein binding (93%) occurs in human plasma and repetitive dosing does not lead to accumulation. The half-life is 7–9 h at doses above 5 mg/kg [81]. Telavancin exhibits time-dependent killing [82].

Telavancin and its comparators of vancomycin or beta-lactam agent have been compared in a phase 2 trial for

skin and skin structure infections. Clinical cure rates were similar at 92% for telavancin vs 96% for comparator agents. Microbiologic rates of cure were noted to be 93% in the telavancin group and 95% among the comparator group [83]. 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%) vs comparator agents (78%, $p=0.07$) [83]. Telavancin is currently under assessment in phase 3 trials of hospital-acquired pneumonia. Adverse events associated with telavancin among patients included vomiting, paresthesias, and dyspnea. Laboratory abnormalities included microalbuminemia and decreased platelets [84].

Clinical indications

Skin and soft tissue infections

Skin and soft tissue infections caused by gram-positive cocci range from simple cellulitis to life-threatening necrotizing fasciitis. All of the newer agents have been studied for such infections and found to be efficacious (Tables 1 and 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, quinupristin/dalfopristin, linezolid, daptomycin, tigecycline, and vancomycin, are appropriate choices for 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 coinfected by anaerobic bacteria and aerobic gram-negative bacilli, in addition to gram-positive cocci.

Bone and joint infections

In osteomyelitis and joint infections, gram-positive cocci predominate. *S. aureus*, both MSSA and MRSA, as well as coagulase-negative staphylococci account for greater than 50% of recovered pathogens. Few studies have prospectively investigated the newer antibiotics in these infections [59, 60]. We evaluated 20 patients who received linezolid for osteomyelitis for 6 weeks or more in a retrospective non-comparative study [85]. Fifty-five percent (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 3 with septic joint infections were treated with daptomycin [86, 87]. MRSA was the predominant pathogen in over 75% of patients. Daptomycin was used as salvage therapy; the usual dose was 6 mg/kg per day. Clinical success rate was about 90%; follow-up periods were a year or less.

Limited data have 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 ± rifampin, tigecycline alone, and vancomycin alone [88]. All regimens were effective (about 90%). Untreated rabbits had spontaneous cure of 26% (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 ± rifampin with equivalent outcome [89].

Pneumonia

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 is often due to MRSA. Linezolid was comparable to vancomycin in the therapy of MRSA-associated VAP, although a trend was seen for linezolid superiority [56, 57]. Daptomycin is not indicated for pneumonia [73], while tigecycline is undergoing clinical evaluation. Quinupristin/dalfopristin has been compared to vancomycin for hospital-acquired pneumonia [50]; 171 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. Of 87 isolates, 2 were shown to have decreased susceptibility to quinupristin/dalfopristin during and after treatment.

Intra-abdominal infection

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 carbapenems, quinolones, and aminoglycosides. Quinupristin/dalfopristin has no activity against *E. faecalis*.

Bacteremia and endocarditis

Daptomycin and quinupristin/dalfopristin have been FDA approved for treatment of gram-positive bacteremia. In addition, daptomycin has been approved for use in *S. aureus* right-sided endocarditis [90]. Dalbavancin, line-

Table 1 Indication and profiles of new antimicrobial agents for resistant gram-positive cocci

	Trade name	Class	MRSA	MRSE	PRSP	VRE	BSI	SSTI	HAP	IE	B/JI	CNS	IAA	Adverse effects	Clinical contraindications	Potential indications
Quinupristin/Dalfopristin	Synercid	Streptogramin	+	+	+	a	×	×						Hepatic Venous irritation Arthralgia Myalgias		*Toxoplasma gondii* infections *Listeria*
Linezolid	Zyvox	Oxazolidinone	+	+	+	+	×	×	×		×			Peripheral/optic neuropathy Reversible cytopenia Lactic acidosis Serotonin syndrome		Osteomyelitis +/or septic joint and prosthetic joint infection
Daptomycin	Cubicin	Lipopeptide	+	+	+	+	×	×		×				Myalgias Arthralgias Rise in CPK Myopathy[e]	Lower respiratory tract infections (alveolar surfactant inhibition)	Osteomyelitis +/or septic joint and prosthetic joint infection
Tigecycline	Tygacil	Glycopeptide	+	+	+	+[b]		×					×	Nausea Diarrhea		CNS meningitis due to PRSP *H. influenzae*
Dalbavancin	N/A	Glycopeptide	+	+	+	c	×	×						Diarrhea Constipation Fever Hypokalemia	N/D	N/D
Oritavancin	N/A	Glycopeptide	+	+	+	+		×						N/D	N/D	Bacteremia
Teicoplanin		Glycopeptide	+	+	+	c	×	×						N/D	CNS	Bone and joint infection
Vancomycin	Vancocin Tabs oral	Glycopeptide	+	+	+	d	×	×	×	×	×	×	×	Nephrotoxicity Ototoxicity Red-man syndrome Phlebitis		*C. difficile* Diarrhea
Telavancin	N/A	Lipoglycopeptide	+	+	+	+		×						Taste disturbance Headache Dizziness Venous irritation		

[a] *E. faecium* only
[b] Gram-negative bacteremia other than *Proteus* spp., *Providencia* spp., and *Pseudomonas* spp.
[c] Not Van A-VRE
[d] Not VISA/VRSA (vancomycin-intermediate susceptible *S. aureus*, vancomycin-resistant *S. aureus*)
[e] Avoid coadministration of statins
BSI bloodstream infection, *SSTI* skin and soft tissue infection, *HAP* hospital-acquired pneumonia, *IE* infective endocarditis, *B/JI* bone and joint infection, *CNS* central nervous system infection, *IAA* intra-abdominal abscess

Table 2 Pharmacology of new antimicrobial agents for resistant gram-positive cocci

	Trade name	Class	Dosage	Route of elimination	Dosage adjustments			Pharmacokinetics					Pharmacodynamics
					Renal	Hepatic		$t_{1/2}$ (h)	C_{max} (ug/ml)	D_{vol} (l/kg)	AUL (kg/h per ml)	Protein binding (%)	
Quinupristin/ Dalfopristin	Synercid	Streptogamin	7.5 mg/kg every 8–12 h IV	Hepatic eliminated in feces	N/A	Yes[a]	Q+ D+ +	3±0.5 1±0.2 dosed every 8 h	3.2±0.67 7.9±1.3	N/A N/A	7.2±1.2 10.6±2.2	N/A N/A	AUC/MIC
Linezolid	Zyvox	Oxazolidinone	600 mg every 12 h IV/PO	Hepatic	N/A dose after HD	N/A	IV	4.8±1.7 5.4±20 600 mg every 12 h	15.1±7.5 21.2±5.8	40–50 138±42	81.7±3.1	31	AUC/MIC
Daptomycin	Cubicin	Lipopeptide	4–6 mg/kg daily IV	Renal	Yes[b]	N/A		8–9.0	57	0.1	494	92	AUC/MIC
Tigecycline	Tygacil	Glycopeptide	100 mg IV	Biliary 60%	N/A	Yes[c]		36	0.11	>10	0.9	68	Time>MIC
Dalbavancin	N/A	Glycopeptide	1000 mg IV Followed by 500 mg IV 7 days later 15 mg/kg	Renal 25–45%	Yes	N/D		216 217 day 1 day 8	180→0.16	1871+ day 7	>95		AUC/MIC
Oritavancin	N/A	Glycopeptide	1.5–3 mg Kg/IV daily	Renal <5% in 14 days	No	N/D		144–360	31	N/D	152	90	AUC/MIC
Teicoplanin		Glycopeptide	6–12 mg/kg IV daily after 3–4 loading doses every 12 h	Renal 80%	Yes	No		83–168	43	0.9–1.6	550	90	AUC/MIC
Vancomycin	Vancocin	Glycopeptide	15 mg/kg IV every 12 h	Renal 8–90%	Yes	No		4–8	20–50	0.3	260	10–55	AUC/MIC
Telavancin	N/A	Lipoglycopeptide	7.5/kg IV daily	Renal	Yes	No		7–9	90–96		680		AUC/MIC

[a] Inhibits CYT P 450-3A4
[b] Reduce to every 48 h with creatinine clearance <30 or dialysis, dose after hemodialysis
[c] Child-Pugh C reduce after 100 mg load to 25 mg daily
C_{max} maximum plasma concentration, D_{vol} volume of distribution, *AUC/MIC* area under the serum concentration time curve/minimal inhibitory concentration

Table 3 *In vitro*/animal synergy studies of *Staphylococcus aureus*

Reference number	Combinations	Pathogen	Test method	Interaction	Definition
[100]	Dapto+Vanco	hGISA	E-test	Additive	FIC index >0.5 to ≤
[100]	Dapto+Gent	hGISA	E-test	Additive	FIC index >0.5 to ≤1
			Time-kill	Additive	1to 2-$\log_{10}$ CFU/ml at 24 h
[96]		GISA	E-test	Additive	FIC index >0.5 to ≤1
		MSSA	Time-kill	Enhance 24 h	≥2-log2-$\log_{10}$ CFU/ml
		MRSA	Time-kill	Enhance 4-24 h	≥2-log2-$\log_{10}$ CFU/ml
[101]		MSSA/MRSA	Time-kill	Increased bactericidal activity	The time to 99% kill by 3.8 h to 5.2 h (statistically not significant)
[102]	Dapto+Rif	MRSA	Animal study (vegetation bacterial density)	Superior to monotherapy	The difference of mean bacterial densities between Dapto + Rif and Dapto monotherapy was statistically significant (p=0.006)
[103]	Dapto+Gent+Rif	MRSA	Monocyte-derived macrophages (MDM)	Superior to monotherapy	Greater activity than double or single (p<0.01)
[100]	Linez+Vanco	hGISA	E-test	Additive	FIC index >0.5 to ≤1
[97]		MSSA/MRSA	Time-kill	Antagonistic	Decrease 100-fold at 24/48 h
[92]		MRSA	Checkerboard	Indifferent	
[98]		MRSA	Time-kill	Indifferent	
[104]		MRSA/MSSA	In vitro pharmacodynamic model	Improvement	Increase in kill <2-$\log_{10}$ CFU/ml /MRSE
[97]	Linez+Gent	MSSA/MRSA	Time-kill	Indifferent	
[98]		MRSA	Time-kill	Antagonistic	Increase C.C ≥2-$\log_{10}$ CFU/ml
[101]		MSSA/MRSA	Time-kill	Indifferent	
[97]	Linez+Rif	MSSA/MRSA	Time-kill	Indifferent	
[98]		MRSA	Time-kill	Synergistic	Decrease C.C ≥2-$\log_{10}$ CFU/ml
[105]		MSSA	Experimental endocarditis model	Indifferent	
[104]	Linez+QD	MRSA	In vitro pharmacodynamic model	Enhance	Increase in kill ≥2-$\log_{10}$ CFU/ml
[100]	Q/D+Vanco	hGISA	Time-kill	Synergistic	≥2-$\log_{10}$ CFU/ml at 24 h
		GISA	E-test	Additive	FIC index >0.5 to ≤1
[106]		MRSA/MSSA	Time-kill	Additive	TR:>5-$\log_{10}$ CFU/ml at 24 h
[104]		MRSA	In vitro pharmacodynamic model	Enhance	Increase in kill ≥2-$\log_{10}$CFU/ml
[95]		MSSA/MRSA	Time-kill	Synergistic	Reduction ≥2-$\log_{10}$ CFU/ml at 24 h
[100]	Q/D+Gent	hGISA	E-test	Indifferent	FIC index >0.5 to ≤1
			Time-kill	Indifferent	1to 2-$\log_{10}$ CFU/ml at 24 h
		GISA	E-test	Indifferent	
			Time-kill	Indifferent	
[107]	Q/D+Rif	S.aureus (HM1054, RP13, HM1054R)	Time-kill	Bactericidal	Decrease 3-$\log_{10}$ CFU/ml
			Animal study (IE model)	Bactericidal	Decrease 3-$\log_{10}$ CFU/ml
[108]		MRSA	Time-kill	Synergistic	Decrease ≥2-$\log_{10}$ CFU/ml
[109]	Tige +Vanco	MRSA	Checkerboard	Indifferent	
			Time-kill	Indifferent	
[110]	Tige+Gent	MRSA	Time-kill	Enhance	>100-fold or >in kill at 24 h
		GISA	Time-kill	Improve	≤100-fold
[109]	Tige+Rif	MRSA	Checkerboard	Indifferent	
			Time-kill	Indifferent	
[111]	Levo+Rif	MSSA	Time-kill	Indifferent	Mean CFU at 72 h was ind.
		MRRA	Time-kill	Indifferent	Mean CFU at 72 h was ind.
[104]		MSSA	Checkerboard	Synergistic	FIC index ≤0.5
		MRSA	Checkerboard	Synergistic	FIC index ≤0.5

Dapto daptomycin, *Linez* linezolid, *Q/D* quinupristin/dalfopristin, *Tige* tigecycline, *Levo* levofloxacin, *Vanco* vancomycin, *Gent* gentamicin, *Rif* rifampin, *hGISA* heterogeneous glycopeptide-intermediate *Staphylococcus aureus*, *TR* total reduction, *C.C* colony count, *FIC* fractional inhibitory concentration, *Enhance* enhancement, *Improve* improvement

zolid, tigecycline, and oritavancin have not yet been approved for bacteremia due to gram-positive cocci.

Linezolid has been evaluated for gram-positive bacteria [58, 91, 92]; in 108 bacteremic patients receiving linezolid, eradication was seen in 91% and clinical cure was seen in 94% [58]. On the other hand, it is not approved for catheter-related bacteremia or endocarditis. A randomized study of linezolid vs vancomycin was conducted in 726 patients with catheter-related bacteremia. An excess number of deaths were seen for patients receiving linezolid due mainly to gram-negative rods implicated in these infections [93]. Based on 23 case reports and 3 case series, a total of 63% (21/33) of patients with endocarditis were cured with linezolid [94]. MRSA and vancomycin-intermediate *S. aureus* were the most commonly isolated gram-positive cocci (24.2 and 30.3% of cases, respectively). Five patients received linezolid monotherapy.

Synergistic interaction of newer antibiotics: *in vitro* studies

In vitro interactions between the new antistaphylococcal antibiotics were virtually always indifferent (additive), although a few showed synergy based on a single study (Table 3). Synergistic interaction was found for quinupristin/dalfopristin plus vancomycin in two independent studies [95, 96]. Antagonistic interactions were demonstrated for the combination of linezolid plus vancomycin [97] and linezolid plus gentamicin [98]. It should be emphasized that *in vitro* interaction may not translate into clinical efficacy. Quinupristin/dalfopristin in combination with vancomycin appeared to be favorable for treatment of MRSA infections responding poorly to vancomycin [99]. The MRSA isolates were of a specific genotype, accessory gene regulator (agr), which has been linked to vancomycin treatment failure [99]. 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.

There will be increased opportunity to use these newer agents due to continued evolution of resistance to the older agents such as vancomycin and for the pharmacodynamic and pharmacoeconomic advantages of these newer agents. As heteroresistance to vancomycin increases, knowledge about the newer antimicrobial agents discussed in this review will become important and useful to clinicians.

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