New Antimicrobial Agents as Therapy For Resistant Gram-Positive Cocci

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Abstract:

Background: Vancomycin and methicillin resistance gram-positive cocci have emerged as an increasingly problematic cause of hospital-acquired infections. Vancomycin resistance has emerged primarily among enterococci but the MIC's of vancomycin are also increasing for staphylococcus species.

Objective: To evaluate the safety and efficacy of newer antibiotics with activity against vancomycin-resistant and methicillin-resistant Gram-positive cocci.

Methods: A literature review was conducted.

Results: Quinupristin-dalfopristin, linezolid, daptomycin, and tigecycline have excellent *in vitro* activity comparable to vancomycin for methicillin-resistant staphylococci and superior to vancomycin for vancomycin-resistant isolates. Dalbavancin, televancin and oritavancin are new glycopeptides with excellent activity against gram positive cocci and have superior pharmacodynamics properties compared to vancomycin. We review the bacterial spectrum, clinical indications and contraindications, pharmacologic properties and adverse events associated with each of these agents.

Conclusions: Daptomycin has rapid bactericidal activity for staphylococcus aureus and is approved use in bacteremia and right-sided endocarditis. It cannot be used to treat pneumonia due to its inactivation in the presence of pulmonary surfactant. Linezolid is comparable to vancomycin in patients with MRSA pneumonia .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 enterococus species and MRSA; it is also active against Enterobacteriaceae and anaerobes which allows for use in intraabdominal and diabetic foot infections.

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* become 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 1960's. 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 1990's 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 1990's, 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 been 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 (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

Re-emergence of Gram- positive cocci have 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 multi-drug resistant pathogen. Resistance to the macrolides, lincosamides, aminoglycosides and all beta-lactam agents are 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 super antigens 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 for endocarditis and osteomyelitis may lead to adverse effects, (especially neutropenia). While VISA/GISA and VRSA infections have only rarely been reported, clinical hetero-resistant populations of VISA (MIC > 4-16 mcg/ml) have been isolated following prolonged duration for vancomycin. Pharmacodynamics of vancomycin may have led to unappreciated under dosing 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 blood stream 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.

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

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 urinary antigen for *S.pneumoniae* are 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 correlate with clinical failure. Specifically, penicillins have been efficacious for pneumonia caused by penicillin-resistant pneumococci [24, 25]. These resistant isolates are often also resistant to

macrolides, and *in vitro* resistance of macrolide does appear to correlate with outcome [26, 27]. 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 suggests that combination therapy may be superior to monotherapy [28].

Groups 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 becteremia. *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 introduction into the United States, the following antibacterial agents have been approved: quinupristin /dalfopristin (Synercid®, Monarch Pharmaceuticals, Inc.) [29-32], linezolid (Zyvox® Pfizer, Inc.)[33, 34], daptomycin (Cubicin®, Cubist Pharmaceutical)[35-37] and tigecycline (Tygacil®, Wyeth Pharmaceuticals, Inc.) [38, 39]. Glycopeptides under study include dalbavancin (BI 397, Pfizer, Inc.) [40], telavancin (TD-6424, Theravance) and oritavancin (Targanta)[41].

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 increasing enzymatic modification, active transport of efflux mediated by an adenosine triphosphate-binding proteinm and alteration of the target site. Resistance is rare for streptococci and *Enterococcus faecium* [42]. Combination acts synergistically to inhibit bacterial protein synthesis at the ribosome level.

Quinupristin/dalfopristin is active against *Staphylococcus aureus*, including MRSA, *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*. 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. Post antibiotic effect is observed at 4-5 hours at 4X MIC versus staphylococci, 7-9 hours for streptococci, and only 4 hours for enterococci [43].

Clinical indications for quinupristin/dalfopristin include intraabdominal infections, bacteremia, urinary tract infection and skin and soft tissue infections in which enterococcus may be a pathogen. Overall clinical success rate for patients with vancomycin-resistant *E. faecium* (VREF) was 74%, while overall clinical and bacteriological success rate was 66% [44]. Patients with bacteremia, on a mechanical ventilator, and undergoing surgery had a worse outcome as might be expected [44]. 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 [45]. 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 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]. 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 54%.

Quinupristin/dalfopristin has been used to treat patients infected by *S. aureus* intolerant of or failing standard therapies [48]. 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. Infections 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% [49, 50]

Linezolid (Zyvox®, 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 23 Sr RNA gene [46]. 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 hours 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 [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 on utility of linezolid for either bacteremia [55] or osteomyelitis [56, 57]. Based on a rabbit model, linezolid does not have sufficient CSF penetration and is not recommended for pneumococcal meningitis [33]. However, CNS penetration appears adequate to treat CSF shunt infections [58].

The cytopenias especially thrombocytopenia is the most common serious adverse effect [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 of greater than 28 days [64, 65]. Lactic acidosis has also been reported and is not associated with duration of usage [65, 66]. 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, pethidne, duloxetine, venlafaxine, milnacipran, sibutramine, chlorpeniramine, brompheniramine, cyproheptadine, citalopram, paroxetine [65, 67]. 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.

The drug is highly protein bound (92%) with a t ½ of 8 hours allowing for once daily dosing. Post-antibiotic effect was dose dependent and reduced in the presence of albumin. Volume of distribution is low (0.1L/kg) and C max (54.6mcg/ml) unchanged at steady state is achieved by day 3 of therapy. C max occurs at the end of a 30 minute infusion. Dosage needs to be reduced and dosing interval extended to every 48 hours in patients with reduced creatinine clearance <30ml/min; and for patients on either hemodialysis or peritoneal dialysis; the dose is 4mg/kg every 48 hours. Daptomycin should be administered after hemodialysis as approximately 15% is cleared per 4 hour hemodialysis session. No adjustments for hepatic dysfunction are required.

In early clinical trails in the 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 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 [68] and to 6 mg/kg daily for bacteremia and endocarditis [69]. 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 [70]. 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 [38]. Resistant clinical isolates were associated with up-regulation of chromosomially mediated efflux pumps. Unlike other tetracyclines, tigecycline has a large volume of distribution (>10L/kg), protein binding is approximately 68%, the t ½ is 36 hours 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 intraabdominal 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, Providentia spp* and *Burkholderia* is = 8mcg/ml which limits its utility in infections caused by those pathogens.

Tigecycline needs no reduction in renal impairment and it 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 [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 cytochrome P450 isoforms: IA2, 2C8, 2C9, 2C19, 2D6 and 3A4.

Dalbavancin (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 1000mg IV once followed by 500mg IV 7 days later; t ½ 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 [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% and 94% microbiologic and clinical response respectively was found in an open label phase 2 comparative dosing trial[73]. 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 Therepeutics]

Oritavancin (LY 33328) is a derivative of vancomycin, chloroeremomycin with the substitution of vancosamine by epi-vancosamine. It has a similar spectrum of activity to vancomycin but with consistently lower MIC's < 1mg/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 [74, 75]. 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 equivarent to vancomycin for both clinical and bacteriological cure (about 78%) [76].

Telavancin (Theravance, Inc.)

Televancin 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 [77]. 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 hours at doses above 5 mg/kg [78]. Telavancin exhibit time-dependent killing [79].

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% in 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[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%) vs. 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 patients included vomiting, paresthesias and dyspnea. Laboratory abnormalities included microalbuminemia and decreased platelets [81].

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 (Table 1). 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 co-infected 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 accounts for greater than 50% of recovered pathogens. Few studies have prospectively investigated the newer antibiotics in these infections [56, 57]. We evaluated 20 patients who received linezolid for osteomyelitis for 6 weeks

or more in a retrospective non-comparative study [82]. Fifty-five percent (11 patients) achieved a cure with follow-up periods ranging from 6-49 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 [83, 84]. 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 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 +/- rifampin, tigecycline alone, and vancomycin alone [85]. 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 [86].

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 [53, 54]. Daptomycin is not indicated for pneumonia [70], while tigecycline is undergoing clinical evaluation. Quinupristin/dalfopristin has been compared to vancomycin for hospital-acquired pneumonia [47]; 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. Two of 87 isolates were shown to have decreased susceptibility to quinupristin/dalfopristin during and after treatment.

Intraabdominal Infection

Of the newer antibiotics, only tigecycline has been approved for intraabdominal 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 quinipristin/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 [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]; in 108 bacteremic patients receiving linezolid, eradication was seen in 91% and clinical cure was seen in 94% [55]. On the other hand, it is 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 report and 3 case series, a total of 63% (21/33) of patients with endocarditis were cured

after linezolid administration [91]. MRSA and vancomycin intermediate *S.aureus* were most commonly isolated cocci (24.2% and 30.3% of cases, respectively). 5 cases are received linezolid monotherepy.

SYNERGISTIC INTERACTION OF NEWER ANTIBIOTICS: *IN VITRO* STUDIES

In vitro interaction 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 [92, 93]. 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/daflopristin in combination with vancomycin appeared to be favorable for treatment of MRSA infections responding poorly to vancomycin [96]. 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 with these new agents are indicated for patients with severe, life threatening infections caused by gram-positive cocci.

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 Myralgia		Toxoplasma Gondii infections Listeria
Linezolid	Zyvox	Oxazolidinone	+	+	+	+	×	×	×		×			Peripheral/optic Neuripathy Reversible cytopenia Lactic acidosis Serotonin syndrome		Osteomyelitis +/or septic joint and prosthetic joint infection
Daptomycin	Cubicin	Lipopeptide	+	+	+	+	×	×		×				Myralgias 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 Vernous irritation

Footnote
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 co-administration of statins

BSI: Blood Stream 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					Pharmaco-dynamics
					Renal	Hepatic	t1/2 (hrs)	CMAX (ug/ml)	DVOL (L/kg)	AUL (kg.h/ml)	Protein Binding (%)	
ıupristin/ opristin	Synercid	Streptogamin	7.5mg/kg every 8-12 hrs IV	Hepatic eliminated in feces	N/A	Yes a	Q+ 3. ± .5 D+ + 1. ± .2 dosed every 8 hours	3.2 ± .67 7.9 ± 1.3	N/A N/A	7.2 ± 1.2 10.6 ± 2.2	N/A N/A	AUC/MIC
ezolid	Zyvox	Oxazolidinone	600mg Every 12hrs IV/PO	Hepatic	N/A dose after HD	N/A	IV 4.8 ± 1.7 5.4 ± 20 600mg every 12 hours	15.1 ± 7.5 21.2 ± 5.8	40-50 138 ± 42	81.7 ± 3.1	31	AUC/MIC
tomycin	Cubicin	Lipopeptide	4-6mg/kg daily IV	Renal	Yes b	N/A	8-9.0	57	0.1	494	92	AUC/MIC
cycline	Tygacil	Glicopeptide	100mg IV	Biliary 60%	N/A	Yes c	36	0.11	>10	0.9	68	Time>MIC
ıavancin	N/A	Glycopeptide	1000mg IV Followed by 500mg IV 7 days later	Renal 25-45%	Yes	N/D	216 217 day1 day8	180?	0.16 day7	1871+	>95	AUC/MIC
avancin	N/A	Glycopeptide	15mg/kg 1.5-3mg Kg/IV daily	Renal<5% in 14days	No	N/D	144= 360	31	N/D	152	90	AUC/MIC
oplanin		Glycopeptide	6-12mg/kg IV daily after 3-4 loading doses every 12 hrs	Renal 80%	Yes	No	83-168	43	0.9-1.6	550	90	AUC/MIC
comycin	Vancocin	Glycopeptide	15mg/kg IV every 12 hrs	Renal 8-90%	Yes	No	4.-8	20-50	0.3	260	10-55	AUC/MIC
vancin	N/A	Lipoglycopeptide	7.5/kg IV daily	Renal	Yes	No	7-9	90-96		680		AUC/MIC

Footnotes
a: Inhibits CYT P 450-3A4
b: Reduce to every 48 hours with Creatinine clearance <30 or dialysis, dose after hemodialysis
c: Child Pugh C reduce after 100mg load to 25mg daily

CMAX: Maximum plasma concentration
DVOL: Volume of distribution
AUC/MIC: Area Under the serum concentration time Curve / minimum inhibitory concentration

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

Reference number	Combinations	Pathogen	Test method	Interaction	Definition
97	Dapto+Vanco	hGISA	E-test	Additive	FIC index >0.5 to =
97	Dapto+Gent	hGISA	E-test Time-kill	Additive Additive	FIC index >0.5 to =1 1to 2-$\log_{10}$ CFU/ml at 24h
93		GISA MSSA MRSA	E-test Time-kill Time-kill	Additive Enhance 24h Enhance 4-24h	FIC index >0.5 to =1 =2-log2-$\log_{10}$ CFU/ml =2-log2-$\log_{10}$ CFU/ml
98		MSSA/MRSA	Time-kill	Increased bacteriocidal activity	The time to 99% kill by 3.8h to 5.2h (statistically not significant)
99	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).
100	Dapto+Gent+Rif	MRSA	Monocyte -derived Macropharges (MDM)	Superior to monotherapy	Greater activity than double or single (p<0.01)
97	Linez+Vanco	hGISA	E-test	Additive	FIC index >0.5 to =1
94		MSSA/MRSA	Time-kill	Antagonistic	Decrease 100-hold at 24/48h
89		MRSA	Checkerboard	Indifferent	
95		MRSA	Time-kill	Indifferent	
101		MRSA/MSSA /MRSE	In vitro pharmaco-dynamic model	Improvement	Increase in kill <2-$\log_{10}$ CFU/ml
94	Linez+Gent	MSSA/MRSA	Time-kill	Indifferent	
95		MRSA	Time-kill	Antagonistic	Increase C.C =2-$\log_{10}$ CFU/ml
98		MSSA/MRSA	Time-kill	Indifferent	

94	Linez+Rif	MSSA/MR SA	Time-kill	Indifferent	
95		MRSA	Time-kill	Synergistic	Decrease C.C =2-$\log_{10}$ CFU/ml
102		MSSA	Experimental endocarditis model	Indifferent	
101	Linez+QD	MRSA	*In vitro* pharmaco-dynamic model	Enhance	Increase in kill = 2-$\log_{10}$ CFU/ml
97	Q/D+Vanco	hGISA	Time-kill	Synergistic	= 2-$\log_{10}$ CFU/ml at 24h
		GISA	E-test	Additive	FIC index >0.5 to =1
103		MRSA/MSSA	Time-kill	Additive	TR:>5-$\log_{10}$ CFU/ml at 24h
101		MRSA	*In vitro* pharmaco-dynamic model	Enhance	Increase in kill = 2-$\log_{10}$CFU/ml
92		MSSA/MRSA	Time-kill	Synergistic	Reduction =2-$\log_{10}$ CFU/ml at 24h
97	Q/D+Gent	hGISA	E-test	Indifferent	FIC index >0.5 to =1
			Time-kill	Indifferent	1to 2-$\log_{10}$ CFU/ml at 24h
		GISA	E-test	Indifferent	
			Time-kill	Indifferent	
104	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
105		MRSA	Time-kill	Synergistic	Decrease = 2-$\log_{10}$ CFU/ml
106	Tige +Vanco	MRSA	Checkerboard	Indifferent	
			Time-kill	Indifferent	
107	Tige+Gent	MRSA	Time-kill	Enhance	>100-hold or >in kill at 24h
		GISA	Time-kill	Improve	=100-hold
106	Tige+Rif	MRSA	Checkerboard	Indifferent	
			Time-kill	Indifferent	
108	Levo+Rif	MSSA	Time-kill	Indifferent	Mean CFU at 72h was ind.

	MRRA	Time-kill	Indifferent	Mean CFU at 72h was ind.
101				
	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

REFERENCES

1. Foster JK, Lentino JR, Strodtman R, DiVincenzo C. Comparison of in vitro activity of quinolone antibiotics and vancomycin against gentamicin- and methicillin-resistant Staphylococcus aureus by time-kill kinetic studies. Antimicrob Agents Chemother 1986; 30:823-7.
2. Tallent SM, Bischoff T, Climo M, Ostrowsky B, Wenzel RP, Edmond MB. Vancomycin susceptibility of oxacillin-resistant Staphylococcus aureus isolates causing nosocomial bloodstream infections. J Clin Microbiol 2002; 40:2249-50.
3. Sieradzki K, Leski T, Dick J, Borio L, Tomasz A. Evolution of a vancomycin-intermediate Staphylococcus aureus strain in vivo: multiple changes in the antibiotic resistance phenotypes of a single lineage of methicillin-resistant S. aureus under the impact of antibiotics administered for chemotherapy. J Clin Microbiol 2003; 41:1687-93.
4. Murray BE. Vancomycin-resistant enterococci. Am J Med 1997; 102:284-93.
5. Okuma K, Iwakawa K, Turnidge JD, et al. Dissemination of new methicillin-resistant Staphylococcus aureus clones in the community. J Clin Microbiol 2002; 40:4289-94.
6. Schwalbe RS, Stapleton JT, Gilligan PH. Emergence of vancomycin resistance in coagulase-negative staphylococci. N Engl J Med 1987; 316:927-31.
7. Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC. Methicillin-resistant Staphylococcus aureus clinical strain with reduced vancomycin susceptibility. J Antimicrob Chemother 1997; 40:135-6.
8. Appelbaum PC. MRSA--the tip of the iceberg. Clin Microbiol Infect 2006; 12 Suppl 2:3-10.
9. MMWR. Staphylococcus aureus Resistant to Vancomycin-United States 2002. Vol. 51 (26): 565.567RE, 2002.
10. Chang S, Sievert DM, Hageman JC, et al. Infection with vancomycin-resistant Staphylococcus aureus containing the vanA resistance gene. N Engl J Med 2003; 348:1342-7.
11. King MD, Humphrey BJ, Wang YF, Kourbatova EV, Ray SM, Blumberg HM. Emergence of community-acquired methicillin-resistant Staphylococcus aureus USA 300 clone as the predominant cause of skin and soft-tissue infections. Ann Intern Med 2006; 144:309-17.
12. Moellering RC, Jr. The growing menace of community-acquired methicillin-resistant Staphylococcus aureus. Ann Intern Med 2006; 144:368-70.
13. Noskin GA, Rubin RJ, Schentag JJ, et al. The burden of Staphylococcus aureus infections on hospitals in the United States: an analysis of the 2000 and 2001 Nationwide Inpatient Sample Database. Arch Intern Med 2005; 165:1756-61.
14. Rupp ME, Archer GL. Coagulase-negative staphylococci: pathogens associated with medical progress. Clin Infect Dis 1994; 19:231-43; quiz 244-5.
15. Schaaff F, Reipert A, Bierbaum G. An elevated mutation frequency favors development of vancomycin resistance in Staphylococcus aureus. Antimicrob Agents Chemother 2002; 46:3540-8.
16. Chang FY, Peacock JE, Jr., Musher DM, et al. Staphylococcus aureus bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. Medicine (Baltimore) 2003; 82:333-9.

17. Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of Staphylococcus aureus infection. Ann Intern Med 1992; 117:390-8.
18. Becker K, Friedrich AW, Lubritz G, Weilert M, Peters G, Von Eiff C. Prevalence of genes encoding pyrogenic toxin superantigens and exfoliative toxins among strains of Staphylococcus aureus isolated from blood and nasal specimens. J Clin Microbiol 2003; 41:1434-9.
19. Lowy FD. Staphylococcus aureus infections. N Engl J Med 1998; 339:520-32.
20. Sakoulas G, Moellering RC, Jr., Eliopoulos GM. Adaptation of methicillin-resistant Staphylococcus aureus in the face of vancomycin therapy. Clin Infect Dis 2006; 42 Suppl 1:S40-50.
21. Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. Clin Microbiol Rev 2002; 15:167-93.
22. Caiazza NC, O'Toole GA. Alpha-toxin is required for biofilm formation by Staphylococcus aureus. J Bacteriol 2003; 185:3214-7.
23. von Eiff C, Peters G, Heilmann C. Pathogenesis of infections due to coagulase-negative staphylococci. Lancet Infect Dis 2002; 2:677-85.
24. Yu VL, Chiou CC, Feldman C, et al. An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered, and clinical outcome. Clin Infect Dis 2003; 37:230-7.
25. Peterson LR. Penicillins for treatment of pneumococcal pneumonia: does in vitro resistance really matter? Clin Infect Dis 2006; 42:224-33.
26. Lonks JR, Garau J, Gomez L, et al. Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant Streptococcus pneumoniae. Clin Infect Dis 2002; 35:556-64.
27. Schentag JJ, Klugman K.P., Yu V.L., et al. Streptococcus pneumoniae bacteremias: pharmacodynamic correlations with outcome and macrolide resistance: a controlled study (in press). Int J Antimicrob Agents 2007.
28. Greenberg D DR, Klugman K, Madhi SA, Feldman C, Roberts S, Morris A, Chedid MBF, Chiou CC, Yu VL. Streptococcus pneumoniae serotypes causing meningitis in children and adults. 14th Intersci Conf Antimicrob Ag Chemother. Washington, DC., 2004.
29. Carpenter CF, Chambers HF. Daptomycin: another novel agent for treating infections due to drug-resistant gram-positive pathogens. Clin Infect Dis 2004; 38:994-1000.
30. Fenton C, Keating GM, Curran MP. Daptomycin. Drugs 2004; 64:445-55; discussion 457-8.
31. Steenbergen JN, Alder J, Thorne GM, Tally FP. Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections. J Antimicrob Chemother 2005; 55:283-8.
32. Schriever CA, Fernandez C, Rodvold KA, Danziger LH. Daptomycin: a novel cyclic lipopeptide antimicrobial. Am J Health Syst Pharm 2005; 62:1145-58.
33. Moellering RC. Linezolid: the first oxazolidinone antimicrobial. Ann Intern Med 2003; 138:135-42.
34. Birmingham MC, Rayner CR, Meagher AK, Flavin SM, Batts DH, Schentag JJ. Linezolid for the treatment of multidrug-resistant, gram-positive infections: experience from a compassionate-use program. Clin Infect Dis 2003; 36:159-68.

35. LaPlante KL, Rybak MJ. Daptomycin - a novel antibiotic against Gram-positive pathogens. Expert Opin Pharmacother 2004; 5:2321-31.
36. Jeu L, Fung HB. Daptomycin: a cyclic lipopeptide antimicrobial agent. Clin Ther 2004; 26:1728-57.
37. Alder JD. Daptomycin: a new drug class for the treatment of Gram-positive infections. Drugs Today (Barc) 2005; 41:81-90.
38. Livermore DM. Tigecycline: what is it, and where should it be used? J Antimicrob Chemother 2005; 56:611-4.
39. Pankey GA. Tigecycline. J Antimicrob Chemother 2005; 56:470-80.
40. Van Bambeke F, Van Laethem Y, Courvalin P, Tulkens PM. Glycopeptide antibiotics: from conventional molecules to new derivatives. Drugs 2004; 64:913-36.
41. Virginlar N. MA. Glycopeptides (Dalbavancin, Oritavancin, Teicoplanin, Vancomycin). In: Yu VL, ed. Antimicrobial Therapy and Vaccines. Vol. II: Antimicrobial Agents: www.antimicrobe.org, 2004.
42. Hershberger E, Donabedian S, Konstantinou K, Zervos MJ. Quinupristin-dalfopristin resistance in gram-positive bacteria: mechanism of resistance and epidemiology. Clin Infect Dis 2004; 38:92-8.
43. Speciale A, La Ferla K, Caccamo F, Nicoletti G. Antimicrobial activity of quinupristin/dalfopristin, a new injectable streptogramin with a wide Gram-positive spectrum. Int J Antimicrob Agents 1999; 13:21-8.
44. Moellering RC, Linden PK, Reinhardt J, Blumberg EA, Bompart F, Talbot GH. The efficacy and safety of quinupristin/dalfopristin for the treatment of infections caused by vancomycin-resistant Enterococcus faecium. Synercid Emergency-Use Study Group. J Antimicrob Chemother 1999; 44:251-61.
45. Nichols RL, Graham DR, Barriere SL, et al. Treatment of hospitalized patients with complicated gram-positive skin and skin structure infections: two randomized, multicentre studies of quinupristin/dalfopristin versus cefazolin, oxacillin or vancomycin. Synercid Skin and Skin Structure Infection Group. J Antimicrob Chemother 1999; 44:263-73.
46. Meka VG, Pillai SK, Sakoulas G, et al. Linezolid resistance in sequential Staphylococcus aureus isolates associated with a T2500A mutation in the 23S rRNA gene and loss of a single copy of rRNA. J Infect Dis 2004; 190:311-7.
47. Fagon J, Patrick H, Haas DW, et al. Treatment of gram-positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Nosocomial Pneumonia Group. Am J Respir Crit Care Med 2000; 161:753-62.
48. Drew RH, Perfect JR, Srinath L, Kurkimilis E, Dowzicky M, Talbot GH. Treatment of methicillin-resistant staphylococcus aureus infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy. For the Synercid Emergency-Use Study Group. J Antimicrob Chemother 2000; 46:775-84.
49. Carver PL, Whang E, VandenBussche HL, Kauffman CA, Malani PN. Risk factors for arthralgias or myalgias associated with quinupristin-dalfopristin therapy. Pharmacotherapy 2003; 23:159-64.
50. Raad I, Hachem R, Hanna H. Relationship between myalgias/arthralgias occurring in patients receiving quinupristin/dalfopristin and biliary dysfunction. J Antimicrob Chemother 2004; 53:1105-8.

51. Stalker DJ, Jungbluth GL. Clinical pharmacokinetics of linezolid, a novel oxazolidinone antibacterial. Clin Pharmacokinet 2003; 42:1129-40.
52. Weigelt J, Itani K, Stevens D, Lau W, Dryden M, Knirsch C. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother 2005; 49:2260-6.
53. Rubinstein E, Cammarata S, Oliphant T, Wunderink R. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. Clin Infect Dis 2001; 32:402-12.
54. Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant Staphylococcus aureus nosocomial pneumonia. Chest 2003; 124:1789-97.
55. Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet 2003; 42:1411-23.
56. Rayner CR, Baddour LM, Birmingham MC, Norden C, Meagher AK, Schentag JJ. Linezolid in the treatment of osteomyelitis: results of compassionate use experience. Infection 2004; 32:8-14.
57. Razonable RR, Osmon DR, Steckelberg JM. Linezolid therapy for orthopedic infections. Mayo Clin Proc 2004; 79:1137-44.
58. Cook AM, Ramsey CN, Martin CA, Pittman T. Linezolid for the treatment of a heteroresistant Staphylococcus aureus shunt infection. Pediatr Neurosurg 2005; 41:102-4.
59. Rho JP, Sia IG, Crum BA, Dekutoski MB, Trousdale RT. Linezolid-associated peripheral neuropathy. Mayo Clin Proc 2004; 79:927-30.
60. Spellberg B, Yoo T, Bayer AS. Reversal of linezolid-associated cytopenias, but not peripheral neuropathy, by administration of vitamin B6. J Antimicrob Chemother 2004; 54:832-5.
61. Young LS. Hematologic effects of linezolid versus vancomycin. Clin Infect Dis 2004; 38:1065-6.
62. Rao N, Ziran BH, Wagener MM, Santa ER, Yu VL. Similar hematologic effects of long-term linezolid and vancomycin therapy in a prospective observational study of patients with orthopedic infections. Clin Infect Dis 2004; 38:1058-64.
63. Nasraway SA, Shorr AF, Kuter DJ, O'Grady N, Le VH, Cammarata SK. Linezolid does not increase the risk of thrombocytopenia in patients with nosocomial pneumonia: comparative analysis of linezolid and vancomycin use. Clin Infect Dis 2003; 37:1609-16.
64. Kulkarni K, Del Priore LV. Linezolid induced toxic optic neuropathy. Br J Ophthalmol 2005; 89:1664-5.
65. Narita MT, B Yu V,L. Linezolid-associated peripheral and optic neuropathy, lactic acidosid and serotonin syndrome: a review. Pharmacotherapy 2007; in press.
66. Soriano A, Miro O, Mensa J. Mitochondrial toxicity associated with linezolid. N Engl J Med 2005; 353:2305-6.
67. Bernard L, Stern R, Lew D, Hoffmeyer P. Serotonin syndrome after concomitant treatment with linezolid and citalopram. Clin Infect Dis 2003; 36:1197.
68. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis 2004; 38:1673-81.

69. Fowler VG, Cosgrove S. Abrutyn E, *et al.* Daptomycin vs Standard Therapy for Staphylococcus aureus Bacteremia (SAB) and Infective Endocarditis (SAIE). 45th Annual Interscience Congress on Antimicrobial Agents and Chemotherapy. Washington DC, 2005.
70. LaPlante KL, Rybak, M.J. Daptomycin. Antimicrobial Therapy and Vaccines. Vol. II: Antimicrobial Agents: www.antimicrobe.org.
71. Zhanel GG, Homenuik K, Nichol K, et al. The glycylcyclines: a comparative review with the tetracyclines. Drugs 2004; 64:63-88.
72. Raad I, Darouiche R, Vazquez J, et al. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. Clin Infect Dis 2005; 40:374-80.
73. Seltzer E, Dorr MB, Goldstein BP, Perry M, Dowell JA, Henkel T. Once-weekly dalbavancin versus standard-of-care antimicrobial regimens for treatment of skin and soft-tissue infections. Clin Infect Dis 2003; 37:1298-303.
74. Kaatz GW, Seo SM, Aeschlimann JR, Houlihan HH, Mercier RC, Rybak MJ. Efficacy of LY333328 against experimental methicillin-resistant Staphylococcus aureus endocarditis. Antimicrob Agents Chemother 1998; 42:981-3.
75. Gerber J, Smirnov A, Wellmer A, et al. Activity of LY333328 in experimental meningitis caused by a Streptococcus pneumoniae strain susceptible to penicillin. Antimicrob Agents Chemother 2001; 45:2169-72.
76. Giamarellou H ORW, Harris H, Owen S, Porter S, Loutit J. Phase 3 trial comparing 3-7 days of oritavancin vs. 10-14 days of vancomycin/cephalexin in the treatment of patients with complicated skin and skin structure infections (CSSI). In: Program and abstracts of the 43rd interscience conference on antimicrobial agents and chemotherapy, Chicago, IL, September 14-17,2003, 2003. American Society of Microbiology.
77. Barrett JF. Recent developments in glycopeptide antibacterials. Curr Opin Investig Drugs 2005; 6:781-90.
78. Shaw JP, Seroogy J, Kaniga K, Higgins DL, Kitt M, Barriere S. Pharmacokinetics, serum inhibitory and bactericidal activity, and safety of telavancin in healthy subjects. Antimicrob Agents Chemother 2005; 49:195-201.
79. Hegde SS, Reyes N, Wiens T, et al. Pharmacodynamics of telavancin (TD-6424), a novel bactericidal agent, against gram-positive bacteria. Antimicrob Agents Chemother 2004; 48:3043-50.
80. Stryjewski ME, Chu VH, O'Riordan WD, et al. Telavancin versus standard therapy for treatment of complicated skin and skin structure infections caused by gram-positive bacteria: FAST 2 study. Antimicrob Agents Chemother 2006; 50:862-7.
81. Stryjewski ME, O'Riordan WD, Lau WK, et al. Telavancin versus standard therapy for treatment of complicated skin and soft-tissue infections due to gram-positive bacteria. Clin Infect Dis 2005; 40:1601-7.
82. Aneziokoro CO, Cannon JP, Pachucki CT, Lentino JR. The effectiveness and safety of oral linezolid for the primary and secondary treatment of osteomyelitis. J Chemother 2005; 17:643-50.
83. Finney MS, Crank CW, Segreti J. Use of daptomycin to treat drug-resistant Gram-positive bone and joint infections. Curr Med Res Opin 2005; 21:1923-6.

84. Anthony S.J. HM, Angelos E, Stratton CW. Clinical Experience with Daptomycin in Patients with Orthopedic-Related Infections. 43rd Infectious Diseases Society of America Annual Meeting 2005. San Francisco, CA, 2005.
85. Yin LY, Lazzarini L, Li F, Stevens CM, Calhoun JH. Comparative evaluation of tigecycline and vancomycin, with and without rifampicin, in the treatment of methicillin-resistant Staphylococcus aureus experimental osteomyelitis in a rabbit model. J Antimicrob Chemother 2005; 55:995-1002.
86. Howden BP, Ward PB, Charles PG, et al. Treatment outcomes for serious infections caused by methicillin-resistant Staphylococcus aureus with reduced vancomycin susceptibility. Clin Infect Dis 2004; 38:521-8.
87. Fowler VG, Jr., Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med 2006; 355:653-65.
88. Woods CW, Cheng AC, Fowler VG, Jr., et al. Endocarditis caused by Staphylococcus aureus with reduced susceptibility to vancomycin. Clin Infect Dis 2004; 38:1188-91.
89. Chiang FY, Climo M. Efficacy of linezolid alone or in combination with vancomycin for treatment of experimental endocarditis due to methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother 2003; 47:3002-4.
90. FDA. Information for Healthcare Professionals: Linezolid (marketed as Zyvox) March 16, 2007, 2007.
91. Falagas ME, Manta KG, Ntziora F, Vardakas KZ. Linezolid for the treatment of patients with endocarditis: a systematic review of the published evidence. J Antimicrob Chemother 2006; 58:273-80.
92. Kang SL, Rybak MJ. In-vitro bactericidal activity of quinupristin/dalfopristin alone and in combination against resistant strains of Enterococcus species and Staphylococcus aureus. J Antimicrob Chemother 1997; 39 Suppl A:33-9.
93. Tsuji BT, Rybak MJ. Short-course gentamicin in combination with daptomycin or vancomycin against Staphylococcus aureus in an in vitro pharmacodynamic model with simulated endocardial vegetations. Antimicrob Agents Chemother 2005; 49:2735-45.
94. Grohs P, Kitzis MD, Gutmann L. In vitro bactericidal activities of linezolid in combination with vancomycin, gentamicin, ciprofloxacin, fusidic acid, and rifampin against Staphylococcus aureus. Antimicrob Agents Chemother 2003; 47:418-20.
95. Jacqueline C, Caillon J, Le Mabecque V, et al. In vitro activity of linezolid alone and in combination with gentamicin, vancomycin or rifampicin against methicillin-resistant Staphylococcus aureus by time-kill curve methods. J Antimicrob Chemother 2003; 51:857-64.
96. Moise-Broder PA, Sakoulas G, Eliopoulos GM, Schentag JJ, Forrest A, Moellering RC, Jr. Accessory gene regulator group II polymorphism in methicillin-resistant Staphylococcus aureus is predictive of failure of vancomycin therapy. Clin Infect Dis 2004; 38:1700-5.
97. Tsuji BT, Rybak MJ. Etest synergy testing of clinical isolates of Staphylococcus aureus demonstrating heterogeneous resistance to vancomycin. Diagn Microbiol Infect Dis 2006; 54:73-7.
98. LaPlante KL, Rybak MJ. Impact of high-inoculum Staphylococcus aureus on the activities of nafcillin, vancomycin, linezolid, and daptomycin, alone and in combination

with gentamicin, in an in vitro pharmacodynamic model. Antimicrob Agents Chemother 2004; 48:4665-72.
99. Sakoulas G, Eliopoulos GM, Alder J, Eliopoulos CT. Efficacy of daptomycin in experimental endocarditis due to methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother 2003; 47:1714-8.
100. Baltch A RW, Bopp L. et al. Killing of Methicillin-Resistant Staphylococcus aureus by daptomycin, gentamicin, and rifampin, singly and in combination, in broth and in human monocyte-derived macrophages, with and without GM-CSF and Interferon-?Activation. ICACC 2005, Abstract E-1741 2005.
101. Allen GP, Cha R, Rybak MJ. In vitro activities of quinupristin-dalfopristin and cefepime, alone and in combination with various antimicrobials, against multidrug-resistant staphylococci and enterococci in an in vitro pharmacodynamic model. Antimicrob Agents Chemother 2002; 46:2606-12.
102. Dailey CF, Pagano PJ, Buchanan LV, Paquette JA, Haas JV, Gibson JK. Efficacy of linezolid plus rifampin in an experimental model of methicillin-susceptible Staphylococcus aureus endocarditis. Antimicrob Agents Chemother 2003; 47:2655-8.
103. Kang SL, Rybak MJ, McGrath BJ, Kaatz GW, Seo SM. Pharmacodynamics of levofloxacin, ofloxacin, and ciprofloxacin, alone and in combination with rifampin, against methicillin-susceptible and -resistant Staphylococcus aureus in an in vitro infection model. Antimicrob Agents Chemother 1994; 38:2702-9.
104. Zarrouk V, Bozdogan B, Leclercq R, et al. Activities of the combination of quinupristin-dalfopristin with rifampin in vitro and in experimental endocarditis due to Staphylococcus aureus strains with various phenotypes of resistance to macrolide-lincosamide-streptogramin antibiotics. Antimicrob Agents Chemother 2001; 45:1244-8.
105. Sambatakou H, Giamarellos-Bourboulis EJ, Grecka P, Chryssouli Z, Giamarellou H. In-vitro activity and killing effect of quinupristin/dalfopristin (RP59500) on nosocomial Staphylococcus aureus and interactions with rifampicin and ciprofloxacin against methicillin-resistant isolates. J Antimicrob Chemother 1998; 41:349-55.
106. Petersen PJ, Labthavikul P, Jones CH, Bradford PA. In vitro antibacterial activities of tigecycline in combination with other antimicrobial agents determined by chequerboard and time-kill kinetic analysis. J Antimicrob Chemother 2006; 57:573-6.
107. Mercier RC, Kennedy C, Meadows C. Antimicrobial activity of tigecycline (GAR-936) against Enterococcus faecium and Staphylococcus aureus used alone and in combination. Pharmacotherapy 2002; 22:1517-23.
108. Palmer SM, Rybak MJ. Pharmacodynamics of once- or twice-daily levofloxacin versus vancomycin, with or without rifampin, against Staphylococcus aureus in an in vitro model with infected platelet-fibrin clots. Antimicrob Agents Chemother 1996; 40:701-5.