

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 enterococcus 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 occurred¹⁻³. 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 therapy⁵. In the late 1990's, glycopeptide resistance was reported for a coagulase-negative staphylococcus⁶ 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 1997⁷ and more than 100 VISA isolates have been since been reported⁸. 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 described¹⁰, 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 problematic¹¹⁻¹³. Foreign body infections and bacteremia caused by coagulase-negative staphylococci have also increased¹⁴. 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 bactericidal¹⁷.

S aureus is a virulent and invasive pathogen. It produces a variety of pyrogenic toxins and super antigens which contribute to their overall virulence¹⁸. The presence of the Pantone - 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 joints¹⁹. 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 resistance²⁰.

Coagulase-negative staphylococci have the capability to produce a glycocalyx enabling them to attach to prosthetic materials²¹. 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 staphylococci²³. 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 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 monotherapy²⁸.

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 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 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 protein 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 enterococci⁴³.

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 expected⁴⁴. 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 isolated⁴⁵. 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 agents⁴⁶. 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 pneumonia⁴⁷. 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 therapies⁴⁸. 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 gene⁴⁶. 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, pethidine, duloxetine, venlafaxine, milnacipran, sibutramine, chlorpheniramine, 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 $t_{1/2}$ 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 trials 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 Pharmaceuticals, Inc.)

Tigecycline is a glycylicycline 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 chromosomally mediated efflux pumps. Unlike other tetracyclines, tigecycline has a large volume of distribution (>10L/kg), protein binding is approximately 68%, the t _{1/2} 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 age⁷¹. 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_{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 bacteremia⁷² and skin and soft tissue infections⁷³. 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 trial⁷³. 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 (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 equivalent to vancomycin for both clinical and bacteriological cure (about 78%)⁷⁶.

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-life⁷⁷. 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/kg⁷⁸. Telavancin exhibit time-dependent killing⁷⁹.

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 group⁸⁰. 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 platelets⁸¹.

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 study⁸². 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 alone⁸⁵. 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 outcome⁸⁶.

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 pneumonia⁷⁰, while tigecycline is undergoing clinical evaluation. Quinupristin/dalfopristin has been compared to vancomycin for hospital-acquired pneumonia⁴⁷; 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 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 endocarditis⁸⁷. 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 bacteremia 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 infections⁹⁰. 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 monotherapy.

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 failure⁹⁶. 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	M R S A	M R S E	P R S P	V R E	BSI	SSTI	HAP	IE	B/JI	CNS	IAA	Adverse effects	Clinical contraindications	Potential indications
Quinupristin/ Dalfopristin	Synercid	Streptogramin	+	+	+	a	×	×						Hepatic Venous irritation Arthralgia Myalgia		Toxoplasma Gondii infections Listeria
Linezolid	Zyvox	Oxazolidinone	+	+	+	+	×	×	×				×	Peripheral/optic Neuripathy Reversible cytopenia Lactic acidosis Serotonin syndrome		Osteomyelitis +/- septic joint and prosthetic joint infection
Daptomycin	Cubicin	Lipopeptide	+	+	+	+	×	×						Myalgias Arthralgias Rise in CPK Myopathy e	Lower respiratory tract infections (alveolar surfactant inhibition)	Osteomyelitis +/- 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
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- 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						Pharmacodynamics	
				Renal	Hepatic	t1/2 (hrs)	C _{MAX} (ug/ml)	DVOL (L/kg)	AUL (kg.h/ml)	Protein Binding (%)			
rupristin/ opristin	Synercid	Streptogamin	7.5mg/kg every 8-12 hrs IV	Hepatic eliminated in feces	N/A	Yes a	Q+	3.± .5	3.2± .67	N/A	7.2± 1.2	N/A	AUC/MIC
							D+	1.± .2	7.9± 1.3	N/A	10.6± 2.2	N/A	
ezolid	Zyvox	Oxazolidinone	600mg Every 12hrs IV/PO	Hepatic	N/A	N/A	IV	4.8± 1.7	15.1± 7.5	40-50	81.7± 3.1	31	AUC/MIC
tomycin	Cubicin	Lipopeptide	4-6mg/kg daily IV	Renal	Yes b	N/A		5.4± 20	21.2± 5.8	138± 42			AUC/MIC
cycline	Tygacil	Glycopeptide	100mg IV	Biliary 60%	N/A	Yes c		8-9.0	57	0.1	494	92	AUC/MIC
avancin	N/A	Glycopeptide	1000mg IV Followed by 500mg IV 7 days later 15mg/kg	Renal 25-45%	Yes	N/D		36	0.11	>10	0.9	68	Time>MIC
avancin	N/A	Glycopeptide	1.5-3mg Kg/IV daily	Renal<5% in 14days	No	N/D		216	180?	0.16	1871+	>95	AUC/MIC
oplanin		Glycopeptide	6-12mg/kg IV daily after 3-4 loading doses every 12 hrs	Renal 80%	Yes	No		217 day1 day8		day7			AUC/MIC
comycin	Vancocin	Glycopeptide	15mg/kg IV every 12 hrs	Renal 8-90%	Yes	No		144=	31	N/D	152	90	AUC/MIC
vancin	N/A	Lipoglycopeptide	7.5/kg IV daily	Renal	Yes	No		83-168	43	0.9-1.6	550	90	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

C_{MAX}: Maximum plasma concentration

D_{VOL}: 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 1 to 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 $=2\text{-log}2\text{-log}_{10}$ CFU/ml $=2\text{-log}2\text{-log}_{10}$ 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 Macrophages (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-fold at 24/48h
89		MRSA	Checkerboard	Indifferent	
95		MRSA	Time-kill	Indifferent	
101		MRSA/MSSA /MRSE	In vitro pharmacodynamic model	Improvement	Increase in kill $<2\text{-log}_{10}$ CFU/ml
94	Linez+Gent	MSSA/MRSA	Time-kill	Indifferent	
95		MRSA	Time-kill	Antagonistic	Increase C.C $=2\text{-log}_{10}$ 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	<i>In vitro</i> pharmacodynamic model	Enhance	Increase in kill = 2-log ₁₀ CFU/ml
97	Q/D+Vanco	hGISA GISA	Time-kill E-test	Synergistic Additive	= 2-log ₁₀ CFU/ml at 24h FIC index >0.5 to =1
103		MRSA/MSSA	Time-kill	Additive	TR:>5-log ₁₀ CFU/ml at 24h
101		MRSA	<i>In vitro</i> pharmacodynamic 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 GISA	E-test Time-kill E-test Time-kill	Indifferent Indifferent Indifferent Indifferent	FIC index >0.5 to =1 1 to 2-log ₁₀ CFU/ml at 24h
104	Q/D+Rif	S.aureus (HM1054,RP13, HM1054R)	Time kill Animal study (IE model)	Bactericidal Bactericidal	Decrease 3-log ₁₀ CFU/ml Decrease 3-log ₁₀ CFU/ml
105		MRSA	Time-kill	Synergistic	Decrease = 2-log ₁₀ CFU/ml
106	Tige +Vanco	MRSA	Checkerboard Time-kill	Indifferent Indifferent	
107	Tige+Gent	MRSA GISA	Time-kill Time-kill	Enhance Improve	>100-fold or >in kill at 24h =100-fold
106	Tige+Rif	MRSA	Checkerboard Time-kill	Indifferent Indifferent	
108	Levo+Rif	MSSA	Time-kill	Indifferent	Mean CFU at 72h was ind.

101

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

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