Novel antibacterial agents for skin and skin structure infections

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With the continuing development of clinical drug resistance among bacteria and the advent of resistance to the recently released agents quinupristin-dalfopristin and linezolid, the need for new, effective agents to treat multidrug-resistant gram-positive infections remains important. With treatment options limited, it has become critical to identify antibiotics with novel mechanisms of activity. Several new drugs have emerged as possible therapeutic alternatives. This review focuses on agents newly introduced and those presently in clinical development for the treatment of skin and skin structure infections. Linezolid, quinupristin-dalfopristin, and daptomycin have been approved by the Food and Drug Administration for the treatment of skin and skin structure infections. Two newer compounds, oritavancin and dalbavancin, are in clinical development for this indication. In addition, the quinolones moxifloxacin and gatifloxacin recently were approved for cutaneous infections. (J Am Acad Dermatol 2004;50:331-40.)

Learning objective: At the conclusion of this learning activity, participants should be familiar with the modes of action, clinical indications, dosage regimens, and contraindications and cautions for several novel antibacterial agents for skin and skin structure infections.

There has been an alarming increase in the incidence of gram-positive infections, including those caused by resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and drug-resistant pneumococci. While vancomycin has been considered the drug of last defense against gram-positive multidrug-resistant bacteria, the late 1980s saw a rise in vancomycin-resistant bacteria, including vancomycin-resistant enterococcus (VRE). More recently, strains of *S aureus* with intermediate resistance to vancomycin have been isolated.[1] Gram-positive bacteria such as *S aureus* and *Streptococcus pyogenes* are often the cause of skin and skin structure infections that range from mild, uncomplicated pyodermas to complicated infections, including postsurgical wound infections, severe carbunculosis, and erysipelas. The category of uncomplicated infections includes such clinical entities as simple abscesses, impetiginous lesions, furuncles, and cellulitis. The complicated category includes infections either involving deeper soft tissue or requiring significant surgical intervention, such as infected ulcers, burns, and major abscesses, and significant underlying disease states that complicate the response to treatment.

Abbreviations used:

ITT:	intent to treat
MRSA:	methicillin-resistant *Staphylococcus aureus*
VRE:	vancomycin-resistant enterococcus
VREF:	vancomycin-resistant *Enterococcus faecium*

With treatment options limited, it has become critical to identify antibiotics with novel mechanisms of activity. Several new drugs have emerged as possible therapeutic alternatives. These include linezolid, quinupristin-dalfopristin, daptomycin, oritavancin and dalbavancin, and the quinolones moxifloxacin and gatifloxacin.

LINEZOLID

Linezolid (Fig 1) is an oxazolidinone antibiotic, shown to be effective for nosocomial and community-acquired pneumonias, vancomycin-resistant *Enterococcus faecium* (VREF) infections, and skin infections due to certain staphylococcus or strepto-

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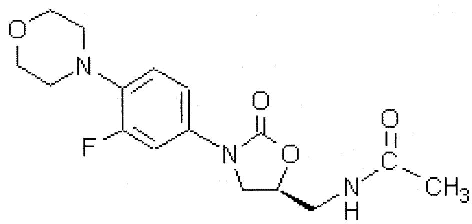

Fig 1. Linezolid.

coccus species.[2] The oxazolidinones are a novel class of antibiotics first discovered in 1987.[3] They are the first new antibiotics to have been discovered in the past 35 years.

Mode of action

Cellular mechanism. Oxazolidinones, and specifically linezolid, are theorized to act by inhibiting the initiation phase of translation and thus interfering with bacterial protein synthesis.[4] It is thought that linezolid binds to the 23S portion of the 50S ribosomal subunit, preventing initiation complex formation. This early inhibition of protein synthesis is a unique mechanism and limits cross-resistance with other antimicrobial agents, since there is no preexisting resistance mechanism in nature.[4]

Pharmacokinetics. Oral bioavailability of the antibiotic in a normal host is 100%. The drug can be administered without regard to meals. Food may decrease slightly the rate of absorption but has no effect on the amount of the drug absorbed. The drug shows a protein binding of only 31% and a half-life of 5 to 7 hours. Linezolid administered orally at 600 mg every 12 hours provides for average steady-state plasma concentrations that exceed MIC90 concentrations for staphylococci, streptococci, and enterococci. It is primarily metabolized by oxidation of the morpholine ring, which produces 2 inactive metabolites. Its metabolism is unaffected by the cytochrome P450 enzyme system. These kinetics do not differ in patients with mild to moderate renal or hepatic compromise. In patients older than 5 years, the 10 mg/kg dose every 12 hours displays similar pharmacokinetic properties.

In vitro activity. In vitro studies have shown linezolid to be effective against many antibiotic-resistant gram-positive organisms, including MRSA, penicillin-resistant *Streptococcus pneumoniae,* and VRE.[5-9] Linezolid is bacteriostatic against most susceptible organisms but has shown bactericidal activity against *Clostridium perfringens, Bacteroides fragilis,* and some strains of *S. pneumoniae.*[10] It has, in addition to its coverage of antibiotic-resistant gram-positive organisms, some broad-spectrum activity against gram-positive cocci, gram-negative anaerobes, and some mycobacteria. It also has shown moderate in vitro inhibitory activity against *Haemophilus influenzae* and *Moraxella catarrhalis,* although it was not effective against Enterobacteriaceae and *Pseudomonas aeruginosa.*

Clinical indications

Linezolid has been approved by the Food and Drug Administration (FDA) for the treatment of various gram-positive infections, including both nosocomial and community-acquired pneumonias, complicated and uncomplicated skin and skin structure infections, and VRE infections. Head-to-head comparisons of the use of linezolid and standard antibiotic therapies in the treatment of skin and soft-tissue infections have been conducted. One study was an evaluation of 332 adult patients with uncomplicated skin infections (cellulitis, skin abscesses, and furuncles) secondary to staphylococcus and streptococcus.[11] In this double-blind, randomized study, linezolid (400 mg twice daily) was compared with clarithromycin (250 mg twice daily) for a course of 7-14 days. After treatment, 91% of the linezolid-treated patients had a clinical cure, compared with 93% in the clarithromycin group. This study showed linezolid to be as effective as clarithromycin.

Another randomized, double-blind, multicenter trial compared the efficacy and safety of linezolid, an oxazolidinone, with those of oxacillin-dicloxacillin in patients with complicated skin and soft-tissue infections.[12] A total of 826 hospitalized adult patients were randomized to receive linezolid (600 mg intravenously) every 12 hours or oxacillin (2 g intravenously) every 6 hours. After sufficient clinical improvement, patients were switched to the respective oral agents, linezolid (600 mg orally) every 12 hours or dicloxacillin (500 mg orally) every 6 hours. Primary efficacy variables were clinical cure rates in both the intent-to-treat (ITT) population and clinically evaluable patients and microbiologic success rate in microbiologically evaluable patients. Safety and tolerability were evaluated in the ITT population. Demographics and baseline characteristics were similar across treatment groups in the 819 ITT patients. In the ITT population, the clinical cure rates were 69.8% and 64.9% in the linezolid and oxacillin-dicloxacillin groups, respectively (P = .141; 95% confidence interval, −1.58 to 11.25). In 298 clinically evaluable linezolid-treated patients, the clinical cure rate was 88.6%, compared with a cure rate of 85.8% in 302 clinically evaluable patients who received oxacillin and dicloxacillin. In 143 microbiologically evaluable linezolid-treated patients, the microbiologic success rate was 88.1%, compared with a success rate of 86.1% in 151 microbiologically evaluable patients who received oxacillin and dicloxacillin. Both agents were well tolerated; most adverse events were of mild-to-moderate intensity. No serious drug-related adverse events were reported in the linezolid group.[12]

Linezolid was also found to be as effective as vancomycin (73.2% vs 73.1%) in a study of the treatment of MRSA infections, in which the most common diagnosis was skin and soft-tissue infections.[13] Other studies also have supported these findings.[14] In addition, a clinical success rate of 81% was noted in cases of infection caused by VRE. There is support that treatment with linezolid may be superior to comparator antibiotics in patients with complicated skin infections that also have comorbid conditions.[15] There have been reports of development of resistance to linezolid in some patients with *Enterococcus faecium*.[16]

Dosage regimens

The recommended dosage of linezolid is dependent on the severity of the skin or soft-tissue infection. The recommended dosage for uncomplicated infections is 400 mg every 12 hours for 10 to 14 days. For complicated infections, 600 mg twice daily either via intravenous infusion or orally is recommended. Because the absolute bioavailability after oral dosing is nearly 100%, no dosage changes are necessary during the switch from intravenous to oral therapy.[4]

Contraindications and cautions

Linezolid is generally well tolerated, the most common adverse effects being diarrhea (8.3%), headache (6.5%), and nausea (6.2%).[10] Since linezolid is a nonselective, reversible inhibitor of monoamine oxidase, it may interact with serotoninergic or adrenergic agents.[17] Like many other antibiotics, it may cause pseudomembranous colitis as a result of overgrowth of *Clostridium difficile*. Approximately 2% of patients may have the development of thrombocytopenia, which appears to be dependent on duration of therapy. The effect is reversible; however, the manufacturer recommends monitoring patients with preexisting thrombocytopenia or patients whose treatment will exceed 2 weeks. No deaths related to thrombocytopenia have been reported.

Conclusions

Linezolid is the first of a novel class of antibiotics called oxazolidinones. Although relatively new, linezolid shows great promise in the treatment of a variety of gram-positive organisms, including MRSA and VRE.

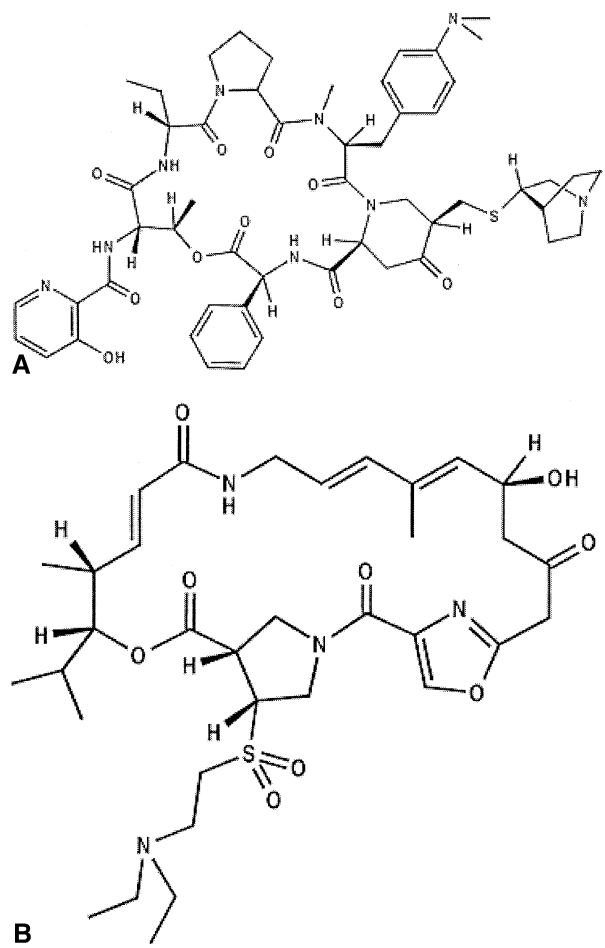

Fig 2. Quinupristin-dalfopristin.

QUINUPRISTIN-DALFOPRISTIN

Quinupristin-dalfopristin (Fig 2) is a combination of 2 semisynthetic pristinamycin derivatives and is the first parenteral streptogramin antibacterial agent. Both quinupristin and dalfopristin have antibacterial capability individually but demonstrate synergistic activity when used in combination. Much of the clinical experience with this antibiotic is derived from 5 comparative trials and an FDA-sanctioned emergency-use program for patients without alternative therapies.

Mode of action

Cellular mechanism. Quinupristin and dalfopristin enter bacterial cells by diffusion and bind to different sites on the 50S ribosomal subunit, resulting in an irreversible inhibition of bacterial protein synthesis.[18] Dalfopristin blocks the reaction catalyzed by the peptidyl transferase catalytic center of the 50S ribosome via inhibition of substrate attachment to the P-site and the A-site of the ribosome. Quinupristin inhibits peptide chain elongation. The synergistic effect of the combination appears to result from these compounds targeting early and late steps in protein synthesis.[19]

Pharmacokinetics. Quinupristin-dalfopristin is rapidly cleared from the blood and is widely distributed. Its elimination is through the bile into the feces. However, its clearance may be slightly reduced in patients with severe chronic renal failure. Its pharmacokinetics are unaffected by age or sex. Quinupristin has a half-life of approximately 1 hour, and dalfopristin has a half-life of approximately 30 minutes. The postantibiotic effect of the drug is prolonged to greater than 7.4 hours against streptococci regardless of penicillin susceptibility.[20] Quinupristin-dalfopristin inhibits the biotransformation rate of cytochrome P450 substrates in vitro.

In vitro. Quinupristin-dalfopristin has inhibitory activity against a broad spectrum of gram-positive bacteria, including MRSA, VREF, and drug-resistant *Streptococcus pneumoniae*. It is bactericidal against methicillin-resistant staphylococci and *S. pneumoniae* and bacteriostatic against most *Enterococcus faecium* in vitro. Quinupristin-dalfopristin also has shown synergy with other antibiotics. Rifampin is synergistic with quinupristin-dalfopristin against MRSA, and doxycycline is synergistic against VREF in vitro.

Clinical indications

FDA indications for quinupristin-dalfopristin are serious infections associated with VREF bacteremia and complicated skin and skin structure infections caused by methicillin-sensitive *Staphylococcus aureus* or *Streptococcus pyogenes*. Treatment of VREF infections is difficult, and few therapeutic options are currently available. These pathogens are resistant to most β-lactam and aminoglycoside antibiotics. Judicious use of vancomycin is currently being advocated to reduce the incidence of resistant organisms, but their presence continues. In 1995, quinupristin was approved for emergency use. During this emergency-use basis in the treatment of VREF infections in which no other treatments were available, quinupristin-dalfopristin had a 71% success rate[21] and a significantly lower mortality than patients using other agents.[22] In another study, patients with complicated skin and skin structure infections who were administered quinupristin-dalfopristin had a clinical success rate (68%) almost identical to that of those using vancomycin, oxacillin, or cefazolin (71%).[23] In addition, in the treatment of patients with gram-positive nosocomial pneumonia, it was found to be as efficacious as vancomycin.[24]

Dosage regimens

For complicated skin or skin structure infections, the recommended dose is 7.5 mg/kg intravenously twice daily for at least 7 days. The drug may be administered up to 3 times daily for bacteremic patients. Dose adjustment to 5 mg/kg is recommended for patients with hepatic insufficiency. No dose adjustment is needed for elderly or renally impaired patients.

Contraindications and cautions

Approximately 63% of patients receiving quinupristin-dalfopristin reported at least 1 adverse effect. Evaluation of these adverse effects is difficult, since it is often done in the context of severe underlying illnesses. Adverse venous events at the intravenous site of administration of the drug were the most common. Reports of pain or inflammation during administration were reported in 34.9% to 74.0% of patients.[23,25] Atrophy, edema, hemorrhage, hypersensitivity, burning, and thrombophlebitis were also reported. A statistically significant number of venous events occurred with quinupristin-dalfopristin, whereas the percentage of such events was much lower with oxacillin, cefazolin, or vancomycin (66.2% versus 28.4%).[21] Suggested but unproved management options to limit these events include administration in a larger volume of fluid or via a central line. Mild to moderate myalgias or arthralgias have been reported.[26] Gastrointestinal events also occurred, with nausea in 4.6%, vomiting and diarrhea in 2.7%, and rash in 2.5%.[27] The most common laboratory abnormalities reported are increases in hepatic transaminases and bilirubin.[27] Quinupristin-dalfopristin is contraindicated in patients with known hypersensitivity to streptogramins and in cases of coadministration with any drugs metabolized by the CYP3A4 enzyme system (some anti-HIV agents, vinca alkaloids, benzodiazepines, immunosuppressives, corticosteroids, and calcium channel blockers). In addition, particular care should be taken when using medications that prolong the Q–T interval (eg, astemizole, cisapride, disopyramide, lidocaine, quinidine, and terfenadine).[27] Caution is also recommended if cyclosporine is being used concomitantly.[28] Resistance to quinupristin-dalfopristin has been encountered infrequently among VREF, and resistance among staphylococci is rare in the United States.[29,30]

Conclusions

Quinupristin-dalfopristin is the first parenteral streptogramin and offers a unique alternative treatment against multidrug-resistant gram-positive bacteria. Because of its potency, bactericidal activity, long postantibiotic effect, and rare resistance, it has excellent potential for treatment of serious gram-positive infections. However, its efficacy should be weighed against possible adverse effects, tolerability, and interactions prior to use of this potent antibiotic. In seriously ill patients with unresponsive infections and minimal other potential treatment options, it should be considered the treatment of choice.

DAPTOMYCIN

Daptomycin (Fig 3) is a novel lipopeptide antibiotic derived from the fermentation of a strain of *Streptomyces roseosporus*. It has shown potent antimicrobial activity against a wide variety of gram-positive bacteria, including MRSA and VRE. Initially developed in the early 1980s, daptomycin was temporarily shelved owing to concerns about skeletal muscle toxicity. At lower doses, this toxicity was not seen, but clinical trials of daptomycin were again halted because of treatment failures in patients with *Staphylococcus aureus* endocarditis. Recently, owing to the need for new agents with activity against vancomycin-resistant bacteria, this intravenous therapy was reevaluated and now has supportive data from phase III clinical trials.[31]

Mode of action

Cellular mechanism. The precise mechanism of action of daptomycin is unknown. It kills by disrupting bacteria plasma membrane function but does not enter the cytoplasm. Proposed mechanisms include inhibition of lipoteichoic acid synthesis[32,33] and dissipation of bacterial membrane potential.[34,35]

Pharmacokinetics. After once-daily dosing, daptomycin exhibits linear pharmacokinetics and minimal accumulation. It has a half-life of approximately 8.5 hours.[36] It is highly protein bound (94%), and its in vitro activity is altered in the presence of serum or albumin.[37,38] Daptomycin is eliminated by the kidney, and therefore dose adjustments based on creatinine clearance are required. Since hepatic metabolism of daptomycin is limited, interactions with other drugs metabolized by the liver are minimal.

In vitro. Daptomycin has rapid, concentration-dependent bactericidal activity against gram-positive organisms. When the standard definition of a 3-log reduction in viable organisms is used, daptomycin and not vancomycin is bactericidal against both *S aureus* and *Enterococcus faecalis*.[39] In addition, in vitro studies designed to evaluate the bactericidal activity of daptomycin, in comparison with vancomycin, linezolid, and quinupristin-dalfopristin, against various gram-positive organisms showed the bactericidal activity of daptomycin to be improved when concentrations are equal to or greater than 4 times the minimal inhibitory concentration.[40] At these levels, daptomycin and vancomycin achieved 99.9% killing of MRSA at 8 hours, which was greater than the killing seen with linezolid and quinupristin-dalfopristin. Daptomycin also had greater activity against VRE at 8 hours and 24 hours than did linezolid and quinupristin-dalfopristin. Spontaneous acquisition of resistance is rare as long as therapeutic serum levels of daptomycin are maintained. Synergistic interactions were noted most frequently with aminoglycosides and against enterococcal organisms.

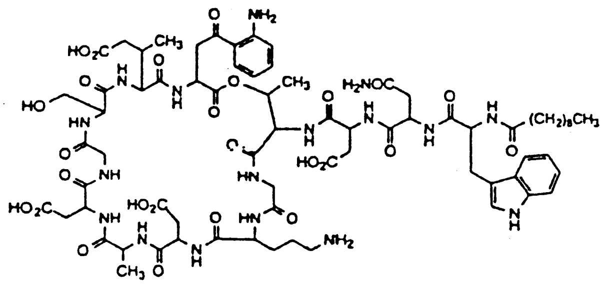

Fig 3. Daptomycin.

Clinical indications

Daptomycin recently was approved for the treatment of complicated skin and skin structure infections caused by gram-positive bacteria, including those caused by MRSA and methicillin-susceptible *S aureus*. In early phase II trials, the clinical efficacy of daptomycin was compared with that of conventional agents such as β-lactams, semisynthetic penicillins, and vancomycin for the treatment of skin infections and bacteremia.[41] In patients with skin and soft-tissue infections, 2 mg/kg daily resulted in clinical cure or improvement in 29 of 30 patients, compared with 37 of 39 patients treated with conventional therapy. Two multicenter phase III trials have now been completed; they involved 1,079 subjects with complicated skin and soft-tissue infections.[31,41] In both studies, the patients were randomized for treatment with intravenous daptomycin (4 mg/kg, once daily) or standard treatment with a semisynthetic penicillin or vancomycin. Of all the clinically evaluable patients, 89% had clinical success with daptomycin, and 88% had successful treatment with standard treatment.[31] These 2 groups were statistically equivalent. Of note, the group that received daptomycin needed a significantly shorter course of treatment, with 63% of patients receiving daptomycin needing only 4-7 days of treatment, while 67% of patients who underwent standard therapy needed 8 or more days of treatment.[31]

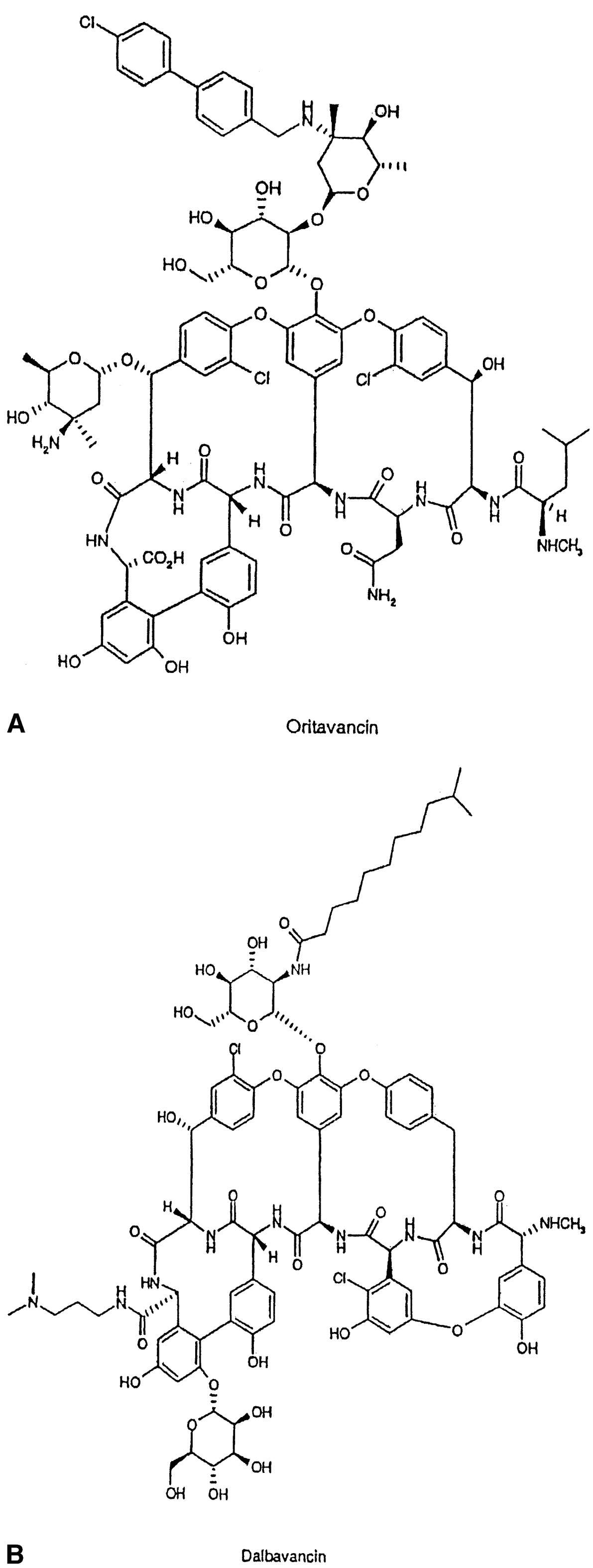

Fig 4. A, Oritavancin. **B,** Dalbavancin.

Dosage regimens

The recommended dosage of daptomycin is 4 mg/kg intravenously every 24 hours for 7 to 14 days.[42] Because daptomycin is eliminated primarily by the kidney, a dosage modification is recommended for patients with creatinine clearance <30 mL/min, including patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. The recommended dosing regimen is 4 mg/kg once every 24 hours for patients with creatinine clearance ≥30 mL/min and 4 mg/kg once every 48 hours for creatinine clearance less than or equal to 30 mL/min, including those undergoing hemodialysis or continuous ambulatory peritoneal dialysis. When possible, daptomycin should be administered after hemodialysis on hemodialysis days.[43]

Contraindications and cautions

Daptomycin is well tolerated, with an incidence and a nature of serious adverse effects comparable to those seen with conventional therapy. The most frequently reported adverse events were headache and constipation in approximately 4% of patients. These events were not dose-related and did not persist. Skeletal muscle has been identified as the primary target organ of daptomycin toxicity.[44] Reversible skeletal muscle toxicity occurred only at the highest dose tested (4 mg/kg every 12 hours). Transient muscle weakness and myalgia were noted but resolved 1 week after the discontinuation of daptomycin. Through the monitoring of creatine phosphokinase levels, muscle toxicity can be prevented, as creatine phosphokinase elevations precede muscle toxicity. No signs of cardiac or smooth muscle toxicity were noted. In addition, once-daily dosing has been shown to minimize associated muscle toxicity.

Conclusions

As resistance to conventional antibiotics increases, daptomycin may be a useful adjunct to our antibiotic armamentarium. It possesses efficacy against resistant bacteria and provides for a rapid and concentration-dependent kill time, a broad spectrum of activity, and a low frequency of resistance. In addition, it is a relatively safe drug with few adverse effects. In February 2003, the FDA accepted a New Drug Application for daptomycin filed by Cubist Pharmaceuticals, Inc.[45]

ANTIBIOTICS IN DEVELOPMENT

Oritavancin (Fig 4, *A*) and dalbavancin (Fig 4, *B*) are 2 novel semisynthetic glycopeptide antibiotics, belonging to the same class as vancomycin. The antibacterial activity of glycopeptide antibiotics results from the inhibition of bacterial cell wall formation. More specifically, these antibiotics inhibit the biosynthesis of bacterial cell wall peptidoglycan.

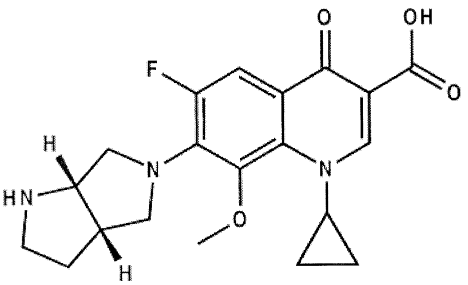

Fig 5. Moxifloxacin.

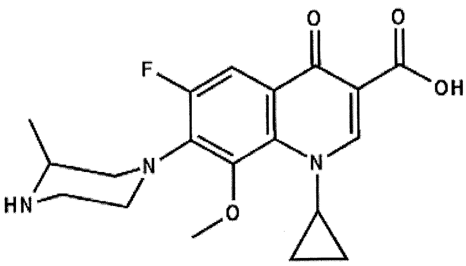

Fig 6. Gatifloxacin.

These 2 agents are currently in late stages of clinical development.

Oritavancin

Oritavancin is distinguished from vancomycin by its bactericidal activity against enterococci, *Streptococcus pneumoniae,* and staphylococci, including MRSA.[45-47] In animal studies that involved rabbits as models, oritavancin was successful in the treatment of endocarditis from MRSA.[48] It also has a longer half-life (>10 days) than vancomycin does and thus can potentially offer a shorter duration of treatment.[49] In a phase III study, intravenous oritavancin (either 1.5 mg/kg or 3.0 mg/kg once daily) followed by placebo was compared with intravenous vancomycin (15 mg/kg once daily) followed by oral cephalexin in 517 patients with complicated skin and soft-tissue infections.* Efficacy was statistically equivalent in the 2 groups, with a 76% clinical success rate in the group that received oritavancin and 80% in patients who received vancomycin and cephalexin. Patients in the oritavancin group required averages of only 5.7 days of treatment for those receiving the 1.5-mg/kg/d dosage and 5.3 days of treatment for the 3.0 mg/kg/d group, compared with 11.5 days for patients receiving vancomycin and cephalexin.* At the end of 2002, a second phase III trial was started to confirm the results from the previous study.† If the results were favorable, InterMune, Inc., planned to file a new drug application with the FDA in 2004.

Dalbavancin

Dalbavancin has also been shown to be bactericidal in in vitro studies with gram-positive pathogens.[50] In animal studies, with rats used as models, dalbavancin was used successfully to treat lobar pneumonia caused by penicillin-resistant pneumococci.[30] In a phase I study with healthy volunteers, subjects received single intravenous infusions of dalbavancin in doses ranging from 70 to 360 mg.[50] Other subjects received dosages of 70 mg per day for 7 days. All single and multiple dosages studied were well tolerated. Dalbavancin was also found to have a long half-life of approximately 10 days.[52] These results suggest that once-weekly dosing could be sufficient to provide trough concentrations that are bactericidal for staphylococcus.[50] In a phase II trial that involved 62 patients with skin and soft-tissue infections, patients underwent 1 of 2 dalbavancin dosing regimens compared with a standard-of-care antibiotic.* Clinical success rates were 94.1% in patients who received 2 doses of dalbavancin, given 1 week apart, 76.2% for standard-of-care treatment (dosing was daily for 7-21 days), and 64.3% for the group that received a single dose of dalbavancin (unpublished data).* In December 2002, Versicor, Inc., announced that it was starting 2 concurrent phase III trials to compare dalbavancin with linezolid and cefazolin-cephalexin in patients with skin and soft-tissue infections.†

NEW INDICATIONS FOR QUINOLONES

The FDA recently added new indications for 2 newer-generation fluoroquinolone-class antibiotics. In April 2001, moxifloxacin (Fig 5) and, in October 2002, gatifloxacin (Fig 6), were approved by the FDA for use in uncomplicated skin and skin structure infections. Several studies supported these new indications. In a multicenter trial that involved 410 patients with uncomplicated skin and soft-tissue infections, a once-daily gatifloxacin dose of 400 mg

*Wasilewski M, Disch D, McGill J, Harris HW, O'Riordan W, Zeckel ML. Equivalence of shorter course therapy with oritavancin compared to vancomycin-cephalexin in complicated skin/skin structure infections. Program and abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; Chicago, Illinois, December 16-19, 2001.

†InterMune completes enrollment for second phase III trial of oritavancin for bacterial skin infections [press release]. Brisbane (CA): InterMune, Inc.; October 24, 2002.

*Versicor announces positive phase 2 study results with dalbavancin for skin and soft tissue infections [press release]. Fremont (CA): Versicor, Inc.; September 5, 2002.

†Versicor begins phase III trials of dalbavancin for skin and soft tissue infections [press release]. Fremont (CA): Versicor, Inc.; December 17, 2002.

Table I. Novel antibacterial agents for skin and skin structure infections

Generic name	Brand name	Mechanism of action	Dosage	Skin infection usage
Linezolid	Zyvox	Binds to 23S portion of 50S ribosomal subunit; prevents initiation complex formation	400–600 mg orally or intravenously every 12 h for 10–14 d	Uncomplicated/ complicated
Quinupristin-dalfopristn	Synercid	Binds to different sites on 50S subunit; inhibits protein synthesis	7.5 mg/kg intravenously every 12 h for at least 7 d	Complicated
Daptomycin	Cubicin	Disrupts bacteria plasma membrane function	4 mg/kg intravenously every 24 h for 10–14 d	Complicated
Oritavancin	—	Inhibits biosynthesis of cell wall peptidoglycan	1.5–3.0 mg/kg intravenously every 24 h for 3–7 d	Complicated
Dalbavancin	—	Inhibits biosynthesis of cell wall peptidoglycan	500–1,000 mg intravenously every wk	Complicated
Moxifloxacin	Avelox	Inhibits DNA gyrase and topoisomerase IV	400 mg orally or intravenously every 24 h for 7 d	Uncomplicated
Gatifloxacin	Tequin	Inhibits DNA gyrase and topoisomerase IV	400 mg orally or intravenously every 24 h for 7–10 d	Uncomplicated

orally had a cure rate of 91%.[51] The control group, which received a once-daily oral dose of 500 mg of levofloxacin, had a cure rate of 84%. Another study examined the efficacy of moxifloxacin versus cephalexin in patients with uncomplicated skin infections.[52] Clinical effectiveness was 90% for the group that received oral moxifloxacin (400 mg once daily) and 91% for the group that received oral cephalexin (500 mg 3 times daily). Both groups received the antibiotics for a total of 7 days. Other studies have also supported these findings.[53]

Conclusions

None of the aforementioned drugs are a solution to antibiotic resistance. However, many of the drugs have shown significant efficacy against previously resistant gram-positive organisms. Linezolid and quinupristin-dalfopristin appear to utilize novel mechanisms of action and may be particularly useful for selected clinical situations for treatment of community-acquired or nosocomial skin and soft-tissue infections. Prudent use of these medications for presumed resistant organisms should be practiced because the development of resistance from overuse is a real concern. Daptomycin also has significant evidence for its efficacy and has been added to the armamentarium against resistant gram-positive skin infections. Novel medications, including oritavancin and dalbavancin, are currently in late stages of clinical development. These medications, with their bactericidal activity, may be a very good option to fight serious gram-positive skin infection in the future. Finally, the fluoroquinolones moxifloxacin and gatifloxacin, which have been on the market for a few years, are now FDA-approved for the indication of uncomplicated skin and soft-tissue infections. Because of their once-daily dosing and tolerability, they appear to be excellent choices for many skin infections. Table I provides a summary of the features of these novel antibacterial agents for skin and skin structure infections.

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Answers to CME examination

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1. c	12. c	23. b
2. d	13. a	24. b
3. c	14. b	25. c
4. e	15. d	26. a
5. e	16. a	27. e
6. a	17. c	28. d
7. e	18. b	29. e
8. b	19. d	30. b
9. c	20. e	31. c
10. a	21. a	32. a
11. b	22. c	33. d