REVIEW

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Two new treatment options for infections due to drug-resistant gram-positive cocci

ABSTRACT

Gram-positive cocci, including enterococci and *Staphylococcus aureus*, have become the leading cause of hospital-acquired infections, and their resistance to antibiotics is increasing. Two important new drugs—quinupristin/dalfopristin (Synercid) and linezolid (Zyvox)—were designed specifically to treat infections due to drug-resistant gram-positive cocci. But their use must be tempered by their cost, toxicity, and concerns about further development of resistant strains.

KEY POINTS

For every person with full-blown vancomycin-resistant enterococci infection, 10 more are colonized.

The decision whether to use quinupristin/dalfopristin or linezolid and which to use depends on the organism, the location and severity of the infection, and other factors.

At least 10% of patients receiving quinupristin/dalfopristin experience arthralgia or myalgia. Phlebitis is also common, necessitating a central line for long-term use.

Myelosuppression occurs in fewer than 10% of patients receiving linezolid. Monitoring of blood counts is recommended.

Drug-resistant isolates have already emerged during therapy with quinupristin/dalfopristin and with linezolid, and they have sometimes been associated with failure of therapy.

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TWO NEW ANTIBIOTICS—quinupristin/dalfopristin (Synercid) and linezolid (Zyvox)—are welcome and needed options for treating gram-positive drug-resistant infections, but they should not be used empirically.

Infections due to gram-positive, drug-resistant organisms such as vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) are on the rise. Although the new drugs were designed specifically to deal with these organisms, they may be associated with serious side effects, they are expensive, and organisms are already becoming resistant to them.

Rational antibiotic use, coupled with awareness of infection control measures, may help to reduce the development of resistance among gram-positive cocci.

This article provides an update of trends in microbial resistance and describes the two new antibiotics, along with several others in development.

SCOPE OF RESISTANCE IN GRAM-POSITIVE COCCI

Twenty years ago, the impetus for antimicrobial drug development was the increasing prevalence of resistance among gram-negative pathogens such as *Pseudomonas aeruginosa*. The pharmaceutical industry responded by developing broad-spectrum antibiotics with enhanced activity against these pathogens, eg, third-generation cephalosporins, quinolones, and extended-spectrum penicillins.

Times have changed. Now gram-positive cocci such as staphylococci, streptococci, and

TABLE 1

Factors leading to establishment and spread of vancomycin-resistant enterococci

Antimicrobial pressure
Suboptimal clinical laboratory recognition and reporting
Unrecognized ("silent") carriage and prolonged fecal carriage
Environmental contamination and survival
Intrahospital and interhospital transfer of colonized patients
Introduction of unrecognized carriers from community settings
Inadequate compliance with handwashing and barrier precautions

ADAPTED FROM MARTONE WJ. SPREAD OF VANCOMYCIN-RESISTANT ENTEROCOCCI: WHY DID IT HAPPEN IN THE UNITED STATES? INFECT CONTROL HOSP EPIDEMIOL 1998; 19:539–545.

enterococci are the leading cause of nosocomial infections, and they are becoming more antibiotic-resistant.

Vancomycin-resistant enterococci (VRE) on the rise

At least 25% of enterococci in the ICU are VRE

The first vancomycin-resistant enterococci (VRE) were isolated in France in 1986.[1] In the United States the rate of resistance rose alarmingly in the 1990s: by 1999, 25.2% of enterococcal isolates from patients in intensive care units were resistant to vancomycin, a 43% increase over rates from 1994 to 1998.[2]

Of the five vancomycin-resistant enterococcal phenotypes, vanA and vanB are the most common.[3] The gene clusters that confer resistance are transferable to other species, and the spread of vancomycin resistance to other pathogens has been demonstrated in vitro.[3]

VRE are almost always *Enterococcus faecium*; on the other hand, *E faecalis* is rarely resistant to vancomycin.

Several factors are promoting vancomycin resistance (TABLE 1),[4] but a major factor is the widespread use of broad-spectrum antibiotics.[5] And not just vancomycin: although vancomycin exerts selective pressure for the development of VRE, cephalosporins and antianaerobic agents are playing an increasingly important role in promoting colonization and infection.[6,7] Inhibition of competing bacteria, particularly by antianaerobic antibiotics with extensive biliary excretion, apparently accounts for VRE overgrowth.[7]

Infections are just the tip of the iceberg: for every person with a full-blown VRE infection, 10 more are colonized, silently carrying the organism without symptoms.[8] The intestinal tract is the primary site of VRE colonization, but many VRE-positive cultures from other sites also represent colonization rather than infection.

In the hospital, the risk of acquiring VRE increases with prolonged hospitalization, proximity to a colonized patient, and contact with health care personnel who care for colonized patients. Contamination of various inanimate objects may also contribute.

Colonization is not an indication for treatment. Moreover, a significant number of true VRE infections resolve with interventions (eg, abscess drainage, debridement, or removal of an infected catheter) without specific antibiotic therapy.

Patients at risk of VRE infection include organ transplant recipients, intensive care patients, and those with cancer or other severe underlying conditions.[9,10] The same groups are also more likely to be colonized with VRE, due to prolonged hospitalization and treatment with broad-spectrum antibiotics, so it may be difficult to determine which patients are most at risk for progression from colonization to infection.

Methicillin-resistant *S aureus* (MRSA): Becoming resistant to vancomycin, too

MRSA strains were recognized in the 1960s. By 1999, more than 50% of *S aureus* isolates in US intensive care units were resistant to methicillin.[2] In the last 5 years, outbreaks of serious MRSA infections have occurred in the community as well,[11,12] illustrating the changing epidemiology of this increasingly common pathogen.

And now these organisms are becoming resistant to vancomycin, too. When vancomycin tolerance was demonstrated in clinical MRSA isolates in Japan and the United States in 1996,[13–15] the worst fears of the medical community were realized: an extremely virulent microorganism had acquired the means to elude the action of the drug that has

been the mainstay of therapy against it.

These strains are called glycopeptide-intermediate *S aureus* (GISA), because they are resistant at an intermediate level to all glycopeptides, including vancomycin and teicoplanin. Intermediate resistance to vancomycin is defined as a minimum inhibitory concentration (MIC; the lowest concentration of vancomycin that inhibits bacterial replication in vitro—the lower the better) of 8 µg/mL, and resistance is defined as an MIC of 16 µg/mL. An MIC of 4 µg/mL should raise the suspicion of intermediate glycopeptide resistance, and the isolate should undergo additional testing.[16]

Detecting vancomycin resistance in the laboratory may be difficult. For example, in an outbreak in Manchester, England,[17] several patients with bacteremia due to an epidemic MRSA strain continued to have positive blood cultures for *S aureus* more than 1 week after starting vancomycin treatment. This suggested that the strain was resistant to vancomycin, even though it was fully susceptible to it in routine laboratory testing. Intermediate resistance to vancomycin (MIC 8 µg/mL) was demonstrated on serial passage of isolates in nutrient broth with increasing concentrations of vancomycin. The mortality rate in patients treated with both rifampin and vancomycin was 4%, but it was 78% if vancomycin was used alone.[17]

Streptococcus pneumoniae: Becoming resistant to penicillin, other antibiotics

Streptococcus pneumoniae strains that were intermediately resistant to penicillin (MIC 0.1–1 µg/mL) were seen as early as 1967, but highly resistant strains (MIC 2 µg/mL) became an issue only in the past decade.[18]

In 1998, approximately 24% of *S pneumoniae* strains in the United States were intermediately or highly resistant to penicillin, with significant geographic variation: more than one third of isolates in Georgia and Tennessee were found to be penicillin-resistant, compared with 15% in California and New York.[19]

In addition, therapeutic alternatives to penicillin, such as tetracycline, macrolides (including erythromycin), cephalosporins, and trimethoprim/sulfamethoxazole, are becoming less useful as the proportion of *S pneumoniae* strains resistant to them grows (**FIGURE 1**).[20] Quinolone-resistant *S pneumoniae* has been reported in Canada, perhaps due to rising rates of quinolone use.[21] The proportion of *S pneumoniae* strains that were resistant to multiple drugs, including penicillin, grew from 9% in 1995 to 14% in 1998.[19]

Drug resistance in *S pneumoniae*

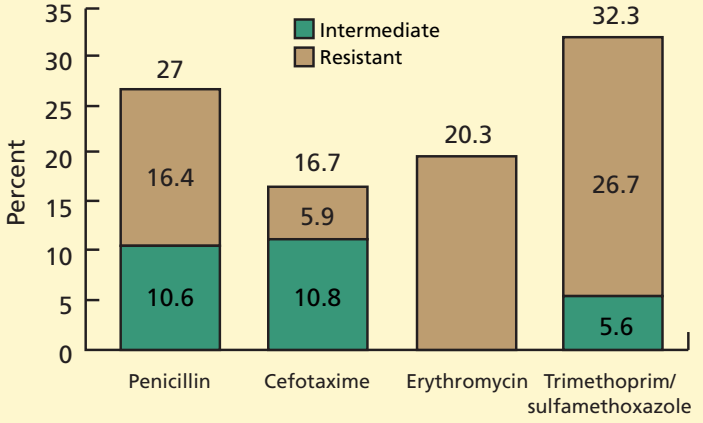


FIGURE 1. Resistance of *Streptococcus pneumoniae* isolates to common antibiotics in the United States

DATA FROM THE CENTERS FOR DISEASE CONTROL AND PREVENTION; HTTP://WWW.CDC.GOV/NCIDOD/DBMD/ABCS/SURVREPORTS/SPNEU99PRELIM.PDF

About 1/4 of *S pneumoniae* are resistant to penicillin

DOES RESISTANCE AFFECT OUTCOME?

We might expect infections to entail higher hospital costs, longer hospital stays, and higher death rates if they are caused by resistant organisms rather than by nonresistant ones, but clinical reality is complex.

Many analyses of the impact of bacterial resistance were limited by difficulties in separating the influence of the patient's underlying conditions from the influence of the pathogen. Other confounding variables include ancillary therapies (eg, concomitant drainage of abscesses, removal of infected prosthetic material) and, for some bacteria, the lack of a gold standard with which new therapies can be compared.

Nevertheless, the bulk of the data seem to indicate that resistant gram-positive infections are costly and deadly.

TABLE 2

General comparison of quinupristin/dalfopristin and linezolid

	QUINUPRISTIN/DALFOPRISTIN	LINEZOLID
Class	Streptogramin	Oxazolidinone
Mechanism	Quinupristin inhibits peptide chain elongation on the 50S ribosome Dalfopristin interferes with peptidyl transferase on the 50S ribosome	Binds to the 23S ribosomal RNA of the 50S subunit Prevents formation of the 70 initiation complex, part of the bacterial translation process
Post-antibiotic effect	Yes (concentration-dependent)	Yes
Synergistic effects	With rifampin against methicillin-resistant *S aureus* With doxycycline, cephalosporins, vancomycin, and ampicillin-sulbactam against VRE	None reported

Mortality rates seem to be higher if the pathogen is resistant

The impact of vancomycin-resistant enterococci

Do VRE infections carry a higher death rate than infections with vancomycin-susceptible enterococci? Studies performed before the advent of anti-VRE antibiotics came to a variety of conclusions.

Although crude mortality rates were consistently higher for patients with VRE bacteremia[22–26] than with non-VRE enterococcal bacteremia, several studies showed that a high APACHE II (Acute Physiology and Chronic Health Evaluation) score was a more important risk factor for death than vancomycin resistance.[23,24]

Linden et al[22] calculated that the enterococcus-associated death rate was 46% in VRE infections vs 25% in bacteremia due to vancomycin-susceptible enterococci. In addition, the length of hospital stay was twice as long for patients with VRE bacteremia.

Edmond et al,[27] in a case-control study of patients with and without VRE bacteremia, calculated the mortality rate attributable to VRE at 37% and the risk ratio for death at 2.3.

The impact of methicillin-resistant *Staphylococcus aureus*

Even though effective therapy is available for MRSA infections, the attributable mortality rate appears to be higher for patients with MRSA infections than with infections due to methicillin-susceptible *S aureus*.

In a modeled analysis of data from New York City hospitals, Rubin et al[28] estimated that the death rate for patients with MRSA infections was 2.5 times higher than with methicillin-susceptible strains of *S aureus*. In addition, hospital costs per patient were approximately 10% higher.

The impact of drug-resistant *Streptococcus pneumoniae*

Feikin et al[29] found that hospitalized patients with pneumococcal pneumonia were five times more likely to die after the second hospital day if the organism was resistant to penicillin or cefotaxime than if it was resistant to neither drug. Fiore et al[30] found that patients with *S pneumoniae* meningitis were more likely to develop neurologic sequelae if the organism was resistant to cefotaxime. In a recent study in New York City, the odds ratio for death among HIV-infected patients was 7.8 if they developed infection due to penicillin-resistant *S pneumoniae*.[31]

OTHER REASONS NEW DRUGS ARE NEEDED

We need new antibiotics to stay ahead of resistant strains, but also because some patients

with drug-susceptible gram-positive infections cannot tolerate first-line therapies. From 6% to 13% of patients receiving vancomycin develop leukopenia,[32,33] 2% develop neutropenia,[34] 3% to 7% develop rash unrelated to infusion,[32,35] and others develop fever, synergistic nephrotoxicity, ototoxicity, or other therapy-limiting side effects.

More difficult to define are the reasons for incomplete or slow responses to vancomycin therapy among some patients. For deep-seated infections such as endocarditis or osteomyelitis due to *S aureus*, the evidence suggests that the addition of a synergistic antibiotic such as rifampin or gentamicin improves the rate of bacterial killing.[36,37] Recent reviews suggest that vancomycin monotherapy may be suboptimal in serious *S aureus* infections.[17,38]

QUINUPRISTIN/DALFOPRISTIN AND LINEZOLID

Quinupristin/dalfopristin (Synercid)[39–41] and linezolid (Zyvox)[42–44] were developed in response to the threat of increasingly resistant enterococci, staphylococci, and pneumococci and concerns about the efficacy and toxicity of vancomycin. Each has distinctive characteristics.

Mechanisms of action

Quinupristin/dalfopristin and linezolid inhibit bacterial protein synthesis on the 50S ribosome (TABLE 2; FIGURE 2).

Quinupristin/dalfopristin is a 30:70 mixture of quinupristin (a group B streptogramin) and dalfopristin (a group A streptogramin). The two components bind to different sites on the bacterial 50S ribosome to form a stable quinupristin-ribosome-dalfopristin tertiary complex, thus inhibiting bacterial protein synthesis.

Linezolid, a oxazolidinone antibiotic, acts early in the process of bacterial protein synthesis by preventing the formation of a functional initiation complex.

Spectrum of antimicrobial activity

Quinupristin/dalfopristin and linezolid are primarily active against gram-positive cocci (TABLE 3).[43,45–48] Both are active in vitro against:

TABLE 3

Antimicrobial activity of quinupristin/dalfopristin and linezolid

BACTERIUM	MINIMUM INHIBITORY CONCENTRATIONS (MIC_{90}; μG/ML) QUINUPRISTIN/DALFOPRISTIN*	LINEZOLID†
Staphylococcus aureus		
Oxacillin-susceptible	0.5	4
Oxacillin-resistant	1	4
Glycopeptide-resistant	1	2
Coagulase-negative staphylococci		
Oxacillin-susceptible	0.5	4
Oxacillin-resistant	0.5	4
Enterococcus faecium		
Vancomycin-susceptible	1	2
Vancomycin-resistant		
Van A	1	2
Van B	1	4
Enterococcus faecalis		
Vancomycin-susceptible	16	2
Vancomycin-resistant	16	4
Streptococcus pneumoniae		
Penicillin-susceptible	0.5	1
Penicillin-resistant	1	1

*The Subcommittee for Antimicrobial Susceptibility Testing of the National Committee for Clinical Laboratory Standards (NCCLS) has set the following interpretive criteria for quinupristin/dalfopristin testing: MIC ≤ 1 μg/mL = susceptible, 2 μg/mL = intermediate, and ≥ 4 μg/mL = resistant.

†Interpretive criteria for linezolid have not been finalized, but the preliminary recommendation is that staphylococcal isolates with an MIC ≤ 4 μg/mL and enterococcal and streptococcal isolates with an MIC ≤ 2 μg/mL are considered susceptible.

- Methicillin-susceptible and methicillin-resistant staphylococci
- Glycopeptide-intermediate *S aureus*
- Vancomycin-susceptible and vancomycin-resistant *E faecium*
- Most streptococci, including penicillin-resistant *S pneumoniae*.

Both drugs also have activity against some bacilli: *Legionella pneumophila*, *Moraxella catarrhalis*, *Listeria monocytogenes*, *Corynebacterium jeikeium*, *Neisseria* species, *Clostridium perfringens*, and *Clostridium difficile*.

Linezolid is active against strains of *E faecalis*, but quinupristin/dalfopristin is not. This difference may influence the choice of empir-

TABLE 4

Pharmacokinetic profiles of quinupristin/dalfopristin and linezolid

	QUINUPRISTIN/DALFOPRISTIN (7.5 MG/KG INTRAVENOUS DOSE)	LINEZOLID (600 MG INTRAVENOUSLY OR ORALLY)
Peak serum level	Quinupristin: 2.6-2.8 µg/mL Dalfopristin: 7.1-8.2 µg/mL	21 µg/mL orally 15 µg/mL intravenously
Half-life	Quinupristin: 0.9-1.1 hours Dalfopristin: 0.4-0.7 hours	4.5-5.5 hours
Metabolism	Hepatic Quinupristin: 2 active metabolites Dalfopristin: 1 active metabolite	Oxidative Two inactive metabolites
Protein binding	Quinupristin: 55%-78% Dalfopristin: 11%-26%	31%
Excretion	Biliary	Renal
Effect of renal dysfunction	None known	Metabolites accumulate Concentrations of parent drug and metabolites reduced by hemodialysis
Effect of liver dysfunction	Metabolites accumulate	None known (not yet tested in patients with severe hepatic insufficiency)

ic anti-enterococcal therapy in some situations.

Neither drug inhibits the growth of enteric gram-negative bacilli.

Pharmacokinetic features

The pharmacokinetics, metabolism, and excretion of quinupristin/dalfopristin and linezolid are summarized in TABLE 4.[39–44]

It is hard to compare the pharmacokinetics of the drugs because quinupristin/dalfopristin is really two drugs, each with unique properties. The effective half-life of the combined product is prolonged by active metabolites and the post-antibiotic effect (continued suppression of bacterial growth despite the decline of the drug concentration to zero).

Quinupristin/dalfopristin is metabolized in the liver and primarily excreted in bile, whereas linezolid undergoes minimal metabolism and is excreted, mostly unchanged, in the urine.

Linezolid is available in oral and intravenous preparations. The oral form is 100% bioavailable.

No dosage adjustment is required for either drug in patients with renal dysfunction. Patients with hepatic insufficiency should probably receive lower doses of quinupristin/dalfopristin because of the potential for accumulation of both the parent compound and metabolites.

Linezolid is active against *E faecalis*, but quinupristin/dalfopristin is not

Drug interactions

Both quinupristin/dalfopristin and linezolid have important drug interactions (TABLE 5).

Quinupristin/dalfopristin inhibits the metabolism of drugs metabolized by the cytochrome P450 3A4 system, which can increase their plasma levels. In particular, serum levels of cyclosporine should be monitored, and drugs metabolized by P450 3A4 that prolong the QTc interval should be avoided; elevated levels of nifedipine and midazolam have been demonstrated.

Linezolid is a reversible, nonselective monoamine oxidase inhibitor and may therefore interact with sympathomimetic, vasopressor, dopaminergic, and serotonergic drugs. Patients taking linezolid should be cautioned about potential hypertensive responses if they

TABLE 5

Drug interactions of quinupristin/dalfopristin and linezolid

Quinupristin/dalfopristin can increase serum levels of*:
- Astemizole
- Cisapride
- Cyclosporine
- Disopyramide
- Lidocaine
- Midazolam
- Nifedipine
- Quinidine
- Terfenadine

Linezolid can induce hypertension by interacting with†:
- Foods and beverages with high tyramine content
- Pseudoephedrine
- Phenylpropanolamine

…or the serotonin syndrome by interacting with:
- Serotonin reuptake inhibitors
- Other antidepressants

*By inhibiting cytochrome P450 3A4
†By inhibiting monoamine oxidase

TABLE 6

Potential adverse effects of quinupristin/dalfopristin and linezolid

	QUINUPRISTIN/DALFOPRISTIN	LINEZOLID
Clinical	Venous irritation Arthralgia, myalgia Nausea, vomiting Diarrhea Rash	Nausea, vomiting Diarrhea Headache Rash Tongue discoloration
Laboratory	Hyperbilirubinemia Elevated hepatic transaminase levels	Thrombocytopenia Leukopenia Anemia Pancytopenia

take cold remedies or decongestants, and the initial doses of adrenergic drugs such as dopamine and epinephrine should be reduced and titrated to effect.

Signs of the serotonin syndrome, such as hyperpyrexia and cognitive dysfunction, may occur with concomitant use of linezolid and nonselective serotonin reuptake inhibitors. Clinical experience in this area is limited.

The oral suspension of linezolid contains 20 mg of phenylalanine per teaspoon, a factor relevant to patients with phenylketonuria.

Adverse effects

Nausea, vomiting, diarrhea, and rash may occur with both quinupristin/dalfopristin and linezolid (TABLE 6).

Quinupristin/dalfopristin. At least 10% of patients receiving quinupristin/dalfopristin experience arthralgia or myalgia or both—a small case-control study put the number at 47%.[49] Another study[50] reported that 9.1% of patients developed arthralgia and that one third of them had to stop taking the drug. The reasons for this reaction are unclear. If it does develop, symptomatic treatment or dose reduction is recommended.

Phlebitis was frequent in clinical trials when quinupristin/dalfopristin was given through peripheral veins.

Laboratory abnormalities associated with quinupristin/dalfopristin are uncommon, but elevated levels of bilirubin and, less commonly, transaminases have been reported.

Linezolid has been associated with myelosuppression.[51] In clinical studies, platelet counts fell to 75% of baseline or less in 3% of patients receiving linezolid, hemoglobin concentrations fell to 75% of baseline or less in 7.1%, and the white blood cell count fell to 50% of baseline or less in 2.2%.[52]

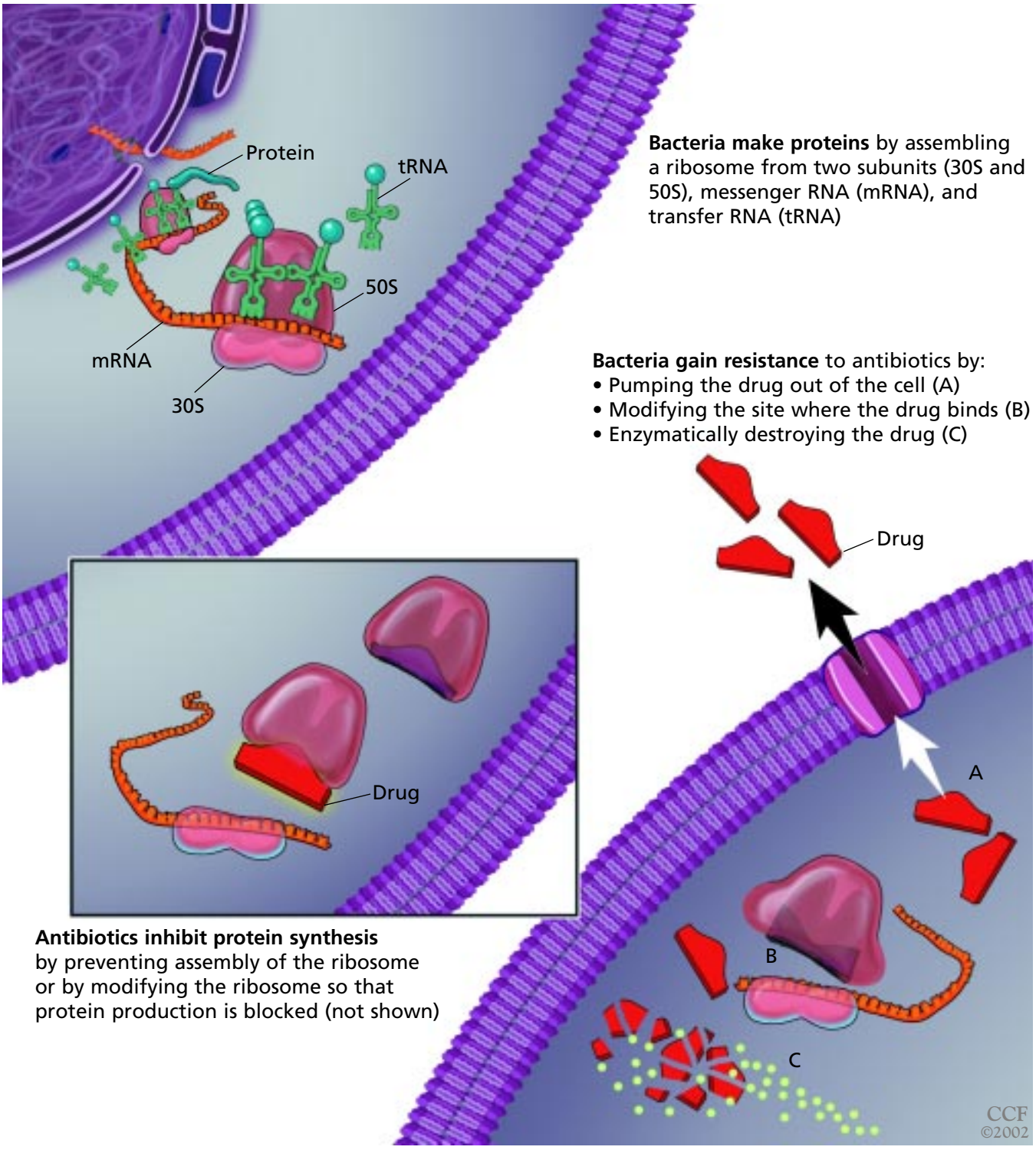
Weekly monitoring of complete blood counts is therefore recommended for patients receiving linezolid, particularly if they receive it for more than 2 weeks, have preexisting myelosuppression, receive concomitant therapy with myelosuppressive drugs or other antibiotics, or have a chronic infection and have previously received antibiotic therapy.[52] The hematologic abnormalities reverse when linezolid is stopped.

Dosage

Quinupristin/dalfopristin is usually given at a dose of 7.5 mg/kg every 8 hours; a dose of 7.5 mg/kg every 12 hours can be used to treat skin and skin structure infections. Each dose should be infused over 60 minutes.

Infusion-related pain and venous irritation are frequent when quinupristin/dalfo-

Antibiotics for gram-positive cocci: How they work, how they fail



Bacteria make proteins by assembling a ribosome from two subunits (30S and 50S), messenger RNA (mRNA), and transfer RNA (tRNA)

Bacteria gain resistance to antibiotics by:
- Pumping the drug out of the cell (A)
- Modifying the site where the drug binds (B)
- Enzymatically destroying the drug (C)

Antibiotics inhibit protein synthesis by preventing assembly of the ribosome or by modifying the ribosome so that protein production is blocked (not shown)

FIGURE 2

pristin is given via peripheral veins, so central venous access is recommended if the patient will receive more than a few days of therapy.

Linezolid is given at a dosage of 600 mg orally or intravenously every 12 hours for most indications, or 400 mg every 12 hours for uncomplicated skin and skin structure infections. When given intravenously, linezolid should be infused over 30 to 120 minutes.

Both quinupristin/dalfopristin and linezolid are physically or chemically incompatible with a number of other intravenous drugs. Quinupristin/dalfopristin is incompatible with saline solutions and with heparin. Linezolid is physically incompatible with amphotericin B, chlorpromazine, diazepam, pentamidine, erythromycin, phenytoin, trimethoprim-sulfamethoxazole, and ceftriaxone.

Indications

Quinupristin/dalfopristin is indicated for:

- Serious or life-threatening infections associated with vancomycin-resistant *E faecium* bacteremia
- Complicated skin and skin structure infections due to methicillin-susceptible *S aureus* or *Streptococcus pyogenes*

Linezolid is indicated for:

- Infections due to vancomycin-resistant *E faecium*, including cases with concurrent bacteremia
- Complicated skin and skin structure infections due to *S aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*
- Uncomplicated skin and skin structure infections due to methicillin-susceptible *S aureus* or *Streptococcus pyogenes*
- Nosocomial pneumonia due to *S aureus* or *S pneumoniae*
- Community-acquired pneumonia due to methicillin-susceptible *S aureus* or penicillin-susceptible *S pneumoniae*.

Linezolid has not been studied in the treatment of decubitus ulcers or diabetic foot infections.

Importantly, because of the restricted antimicrobial spectra of these two drugs, combination therapy may be necessary if gram-negative organisms are either known or suspected to be concurrent pathogens.

Do not mix quinupristin/dalfopristin with saline or heparin

CLINICAL STUDIES OF QUINUPRISTIN/DALFOPRISTIN

Since both quinupristin/dalfopristin and linezolid have been on the market for a relatively short time, reports of their use for the most part reflect studies performed while they were still investigational.

As yet, no study has compared the two drugs head to head, and they cannot be considered therapeutic equivalents.[53,54]

In vancomycin-resistant *E faecium* infections

Moellering et al[50] gave quinupristin/dalfopristin to 396 patients with infections due to vancomycin-resistant *E faecium* under a compassionate-use protocol, often after other therapies had failed.

The patients were seriously ill: their mean APACHE II score was 18.2, and many had renal failure, mechanical ventilation, malnutrition, leukemia, transplantation, or bacteremia at study entry. Sixteen percent had an underlying oncologic disorder. The crude mortality rate was 52.6%. One third of the patients had an intra-abdominal infection; 28.2% had bacteremia of unknown origin.

The overall clinical success rate was 73.6% in patients evaluated clinically, and the bacteriologic response rate was 70.5% in patients undergoing bacteriologic evaluation.[50]

Arthralgia was the most frequently reported adverse reaction (9.1% of patients), and treatment was discontinued in one third of patients who developed arthralgia. Nearly 50% of patients who received quinupristin/dalfopristin through a peripheral venous catheter experienced phlebitis. In vitro resistance to quinupristin/dalfopristin emerged during therapy in 6 of 156 patients evaluated bacteriologically.

In a similar group of 396 patients receiving quinupristin/dalfopristin as part of an emergency-use study,[55] therapy failed in 4 of 5 patients in whom resistance developed.

In skin infections

Nichols et al[56] gave either quinupristin/dalfopristin or a standard antibiotic therapy (cefazolin, oxacillin, or vancomycin) to 893 hospitalized patients with complicated gram-positive skin and skin structure infections, most of

whom had erysipelas, traumatic wound infection, or clean surgical wound infection. *S aureus* was the most common pathogen.

Rates of clinical success (defined as cure and improvement) were equivalent in both groups for skin and soft tissue infections.

More patients (66.2%) had adverse venous events (inflammation, thrombophlebitis, pain, hypersensitivity, hemorrhage, or edema) with quinupristin/dalfopristin than with standard therapies (28.4%). Nausea was reported in 6.2% of patients receiving quinupristin/dalfopristin vs 2.0% in those on standard therapy.

In nosocomial pneumonia, staphylococcal bacteremia

Quinupristin/dalfopristin and vancomycin had similar efficacy against gram-positive nosocomial pneumonia in a multicenter trial of 298 patients.[57] Both agents also produced similar outcomes in patients with catheter-related staphylococcal bacteremia in another study.[58]

In methicillin-resistant *S aureus* (MRSA) infections

Drew et al[59] gave quinupristin/dalfopristin to 90 patients with MRSA infections in whom prior therapy failed or was not tolerable. Forty-four percent of the patients had bone and joint infections. The mean duration of treatment was 28.5 days. The response rate was 71%. The presence of the macrolide-lincosamide-streptogramin type B resistance phenotype did not influence the response rate.

Quinupristin/dalfopristin has been given successfully to patients in home care and other settings outside the hospital.[60]

CLINICAL STUDIES OF LINEZOLID

Published clinical studies of linezolid are limited by small numbers of patients.

In VRE infections

Chien et al[61] gave linezolid to 15 patients with VRE infections. Twelve of the patients were in an intensive care unit when the infection was diagnosed, 6 were on dialysis, and 5 had recently received a liver transplant. Ten had VRE bacteremia, and 4 of the 5 liver transplant patients had VRE peritonitis.

Ten patients completed therapy with linezolid, and all of them achieved a microbiological cure. Eleven patients underwent wound debridement, drainage of an abscess, or removal of an infected prosthetic device. Nonetheless, three patients required a second course of linezolid because of persistent VRE infection. Eight patients died, but none of the deaths was directly attributable to VRE infection. One patient developed nausea and another developed leukopenia during linezolid therapy.

The same study[61] also reported the use of linezolid in two patients who could not tolerate vancomycin: one had an epidural abscess due to methicillin-resistant coagulase-negative staphylococci, and the other had recurrent parotitis due to MRSA. Both were cured with linezolid therapy.

In nosocomial pneumonia

Rubenstein et al[62] performed a randomized trial in which 203 patients with nosocomial pneumonia received the combination of linezolid plus aztreonam and 193 received vancomycin plus aztreonam.

At baseline, a specific pathogen had not been identified in more than one third of patients in each group, and at least 40% were not on mechanical ventilation. The mean APACHE II score at enrollment was 15.7 in the linezolid group and 15.4 in the vancomycin group.

Combination therapy may be necessary if gram-positive and gram-negative organisms are present

The clinical cure rates were similar: 66.4% with linezolid and 68.1% with vancomycin. The microbiological success rates were 67.9% with linezolid and 71.8% with vancomycin.

Four percent of the patients in the linezolid group and 3% in the vancomycin group developed diarrhea. The authors stated "There were no clinically relevant, statistically significant differences between treatments for any hematologic assay."[62] The mean white blood cell and neutrophil counts decreased to normal ranges during the study in both groups, consistent with resolution of infection. None of the 118 patients who received linezolid concomitantly with a sympathomimetic agent had any clinically significant monoamine oxidase inhibitor-like interactions.

Other uses of linezolid

Linezolid compared favorably with ceftriaxone in the treatment of patients hospitalized with community-acquired pneumonia.[63] Success rates with linezolid were also similar to those of standard antibiotics in the treatment of both uncomplicated and complicated skin and skin-structure infections.[63]

In several case reports, linezolid was used to treat a variety of conditions. In one report,[64] linezolid cured long-term VRE bacteremia due to septic thrombophlebitis in a patient with acute myelogenous leukemia; treatment with quinupristin/dalfopristin had failed, even though the isolate remained susceptible.

Other reports have been published of cures in patients with VRE vertebral osteomyelitis, meningitis, and bacteremia.[65–67] Oral linezolid has been used to complete therapy for VRE endocarditis,[68] and it has been used to treat a patient with disseminated *Mycobacterium chelonae* infection.[69]

How bacteria gain resistance to these new antibiotics

Drug-resistant isolates have already emerged during therapy with the new drugs

Bacteria can overcome these drugs, however. Drug-resistant isolates have already emerged during therapy with quinupristin/dalfopristin[40,50,55,70,71] and with linezolid,[43,72,73] and they have sometimes been associated with failure of therapy.[55,71–73]

Bacteria can gain resistance to streptogramins such as quinupristin/dalfopristin in three ways (FIGURE 2):

- By modifying their target binding site (the most common mechanism). Methylation of the 23S ribosomal binding site is associated with staphylococcal resistance to macrolides, lincosamides, and group B streptogramins, such as quinupristin. Group A streptogramins such as dalfopristin, however, are not affected by this mechanism of resistance, and hence retain their bacteriostatic activity. Although resistance to clindamycin and erythromycin may suggest resistance to macrolides, lincosamides, and group B streptogramins, the correlation is imperfect.
- By inactivating the drug. Enzymatic degradation of either quinupristin or dalfopristin may be observed in staphylococci and *E faecium*.
- By pumping the drug out of their cells. Active efflux of dalfopristin may result in the development of resistance among some strains of coagulase-negative staphylococci and *E faecium*.

On the positive side, the rate of emergence of isolates that are fully resistant to quinupristin/dalfopristin may be lower than expected because of the drug's dual sites of action and because an organism would need to acquire several resistance genes before becoming clinically resistant.

Linezolid resistance is also mediated by modification of the target binding site (23S ribosomal mutations). Because linezolid is the only available drug in its class (ie, oxazolidinones), cross-resistance with existing antibiotics is not expected.

WHEN TO USE THE NEW DRUGS

Although quinupristin/dalfopristin and linezolid are active against a wide variety of gram-positive cocci, they are rarely first-line agents. We have little evidence from clinical trials as to their efficacy in infections other than those due to VRE and *S aureus*. They have important potential toxicities, and they are costly (approximately $322 per day for quinupristin/dalfopristin, $144 for intravenous linezolid, and $106 for oral linezolid).

Nevertheless, quinupristin/dalfopristin and linezolid are welcome additions because they are active against resistant organisms and are useful in patients who cannot tolerate standard antibiotics.

The choice of an antimicrobial drug depends on the target organism, the location and severity of the infection, and patient-related factors. For example, VRE infections of the urinary tract may be treated with nitrofurantoin or fosfomycin rather than parenteral systemic agents. Chloramphenicol, either alone or in combination with doxycycline or rifampin, has been effective for treating some VRE infections and offers a less expensive alternative to the new agents; however, its potential for causing hematologic side effects must be considered.

Patients who need empiric antibiotic therapy active against enterococci but who cannot tolerate penicillin or vancomycin may benefit from initial therapy with linezolid because it is effective against both *E faecalis*

and *E faecium*.

In patients with infection due to an organism susceptible to multiple agents, the potential for adverse reactions is an important factor in selecting an antibiotic. The possibility of hematologic side effects may argue against the use of linezolid in patients with preexisting thrombocytopenia and those at risk for bleeding complications. Likewise, the need to place a central catheter or peripherally inserted central catheter for prolonged administration of quinupristin/dalfopristin may lead to the selection of alternative drugs.

INVESTIGATIONAL ANTIBIOTICS

Several drugs that target drug-resistant gram-positive bacteria are under development.

Daptomycin is a parenteral lipopeptide antibiotic that kills gram-positive bacteria, including vancomycin-resistant enterococci, glycopeptide-intermediate *S aureus*, and penicillin-resistant *S pneumoniae*.[74,75] Skeletal muscle toxicity, observed in animals receiving larger doses of daptomycin, has not been observed in recent trials in humans. Administration is once a day. This promising drug is undergoing phase III trials.

LY333328 is another promising glycopeptide antibiotic with spectrum of action similar to that of daptomycin. Clinical trials are underway.

Ramoplanin is an oral glycolipodepsipeptide with a half-life of nearly 1 week. A phase II trial showed that it suppresses VRE carriage in the gastrointestinal tract.[76]

Telithromycin, an oral ketolide, is a potential alternative for treating infections due to macrolide-resistant pneumococci.

FORESTALLING DRUG RESISTANCE

To prevent, treat, and control infections due to resistant gram-positive pathogens, we need a multifaceted approach that involves:

- Enhanced surveillance for and testing of target isolates
- Infection control measures
- Prudent use of antibiotics, both in hospitals and in the community (see patient information, **Using antibioics wisely**, page 414).[77]

Several studies[7,78,79] suggest that antibiotic formulary changes influence rates of isolation of resistant bacteria. Another potential tactic is to cycle or rotate antibiotics in the intensive care unit or other designated institutional setting,[80] although VRE emerged during a study involving scheduled antibiotic rotation in one intensive care unit.[81]

Since many invasive infections are caused by penicillin-resistant *S pneumoniae* strains that are covered by the pneumococcal vaccine, it is hoped that immunization of additional populations will be helpful.[19,31] Work continues on a staphylococcal vaccine. In the meantime, continued development of newer antimicrobial agents active against resistant gram-positive bacteria is necessary.

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