

Methicillin-resistant *Staphylococcus aureus* and Vancomycin-resistant Enterococci: Emerging Problems and New Prospects for Management

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Abstract

Introduction: Infections due to multidrug-resistant Gram-positive bacteria are a growing worldwide problem, particularly among seriously ill patients. A number of studies have demonstrated that patients infected with either methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci (VRE) are at higher risk for mortality and medical resource expenditures. **Methods:** A non-systematic evidence-based review of linezolid, the first commercially available oxazolidinone, and quinupristin/dalfopristin, the first injectable streptogramin, for management of these multidrug-resistant infections was conducted. **Results:** As infections due to VRE increase and vancomycin-insensitive MRSA emerge, vancomycin is becoming less effective for managing Gram-positive infections. Preclinical comparative studies demonstrated that linezolid and quinupristin/dalfopristin are highly effective in eradicating both susceptible and resistant staphylococci, streptococci, and enterococci. Clinical experience, including phase III and compassionate-use data, with these newer agents in the treatment of MRSA and VRE infections are discussed. **Conclusions:** The clinical experiences thus far with linezolid and quinupristin/dalfopristin for MRSA and VRE infections have demonstrated efficacy, making these agents important additions to the limited number of therapeutic alternatives for Gram-positive infections.

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Introduction

The prevalence of nosocomial infections due to Gram-positive bacteria has increased dramatically over the last two decades. In North America, Gram-positive cocci now are responsible for nearly two thirds of all bloodstream¹⁻³ and skin and soft tissue infections.⁴ Another trend that has evolved concurrently is an increased clinical occurrence of multidrug-resistant Gram-positive bacteria among hospitalised patients.^{5,6} The highest antimicrobial resistance rates are documented in bacterial isolates from critically ill patients in intensive care units (ICUs),^{7,8} a patient population at high risk for nosocomial infections.⁹ There are a multitude of hypotheses to account for the emergence of multidrug-resistant staphylococci, streptococci, and enterococci, such as (1) increased use of antimicrobial agents, especially cephalosporins, (2) suboptimal attention to infection control practices, and (3) drug development previously focused on antimicrobial agents with extended-spectrum or Gram-negative activity, thereby permitting slow evolution of Gram-positive bacteria.⁸⁻¹¹

The Gram-positive bacteria most commonly implicated in resistant nosocomial infections are methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), primarily *Enterococcus faecalis* and *E. faecium*. Few antimicrobial agents have had substantial activity against MRSA and VRE, leaving clinicians with limited, if any, therapeutic alternatives. MRSA strains generally are resistant to most other antimicrobial classes, including β -lactams, carbapenems, macrolides, and aminoglycosides.^{10,12} In recent years, widespread resistance to fluoroquinolones has developed among most MRSA strains as well.¹² Enterococci are known to exhibit intrinsic resistance to most antimicrobial classes (e.g., penicillinase-resistant penicillins, cephalosporins) and have acquired resistance to other agents—most notably to vancomycin and the aminoglycosides.^{8,11-13} Vancomycin resistance occurs much more frequently among *E. faecium* compared to *E. faecalis*.^{2,11} The rising prevalence of VRE is alarming, not only because it poses a therapeutic challenge, but also because of the possibility that VRE will transmit

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vancomycin resistance to *S. aureus*.

Two new agents with selective Gram-positive activity were recently approved in the United States—linezolid (an oxazolidinone)¹⁴ and quinupristin/dalfopristin (a streptogramin).¹⁵ Both of these novel agents are highly active against multidrug-resistant staphylococci and enterococci.¹⁶⁻²¹ This review provides an overview of the epidemiology and clinical implications of MRSA and VRE and selected clinical experiences with both linezolid and quinupristin/dalfopristin.

Resistant Gram-positive Bacteria

MRSA

The introduction of semisynthetic penicillins once allowed uniformly successful treatment of *S. aureus* infections; however, MRSA has become increasingly endemic since its initial isolation in the United Kingdom in 1961.^{11,22} MRSA is most prevalent in Japan, with an overall prevalence rate of approximately 60%.²³ A 1990-1991 survey of MRSA in European countries revealed that 13% of *S. aureus* isolates were methicillin resistant, with rates ranging from <1% in Scandinavia to >30% in Spain, Italy, and France.²⁴ According to the National Nosocomial Infections Survey (NNIS), conducted by the Centers for Disease Control and Prevention (CDC), the prevalence of MRSA in ICUs in the United States in 1999 was 43% higher than the mean prevalence for the 5-year period of 1994 to 1998.²⁵ Today, the incidence of MRSA infections among hospitalised patients in ICUs is in excess of 50%.²⁵ The prevalence of MRSA tends to be substantially higher in larger hospitals than in smaller ones, but it appears to be increasing regardless of hospital size.²⁶

S. aureus isolates with reduced susceptibility to vancomycin, in association with treatment failure, were recently identified in the United States,²⁷⁻³⁰ Japan,^{31,32} and France.³³ In all cases, the patients received multiple long-term courses of glycopeptide antibiotics (vancomycin or teicoplanin) for the treatment of MRSA-associated infections. Heterogeneous vancomycin-intermediate *S. aureus* appears to be spreading throughout Japan; in one Japanese study, the overall prevalence was 9.3% in university hospitals and 1.3% in non-university hospitals/clinics.³⁴

It is generally believed that MRSA most commonly enters an institution through a colonised or infected patient transferred from another setting, with subsequent dissemination primarily through person-to-person contact. MRSA transmission through inanimate objects is suspected to occur in units with high contamination rates and patients in close proximity to each other.¹¹ Thus, prolonged hospitalisation, particularly in the ICU, is one of the most important risk factors for MRSA infection. Other patient-

specific risk factors include use of invasive devices and prior antimicrobial therapy or surgery.³⁵ Nasal carriage of MRSA has been identified as a risk factor for the development of MRSA bacteraemia among ICU patients.³⁶ In a study conducted at the University of Barcelona, the adjusted relative risk for *S. aureus* bacteraemia was 3.9-fold higher for MRSA carriers compared with methicillin-sensitive *S. aureus* carriers.³⁶ Such findings have intensified interest in screening for MRSA colonisation on admission and therapies with the potential to eradicate MRSA colonisation, such as mupirocin nasal ointment.

Numerous studies provide evidence that mortality rates for patients with MRSA infections are increased compared with those associated with methicillin-susceptible staphylococcal infections.^{35,37-40} Additionally, the morbidity of MRSA infections appears to translate into more extensive medical resource utilisation. The median hospital stay attributable to primary nosocomial MRSA infection has been reported to be 2- to 3-fold longer than that for patients infected with susceptible staphylococcal strains.^{37,41} This prolonged hospitalisation generally has translated into a 2- to 3-fold increase in medical costs.^{37,42}

VRE

VRE was first reported in the United Kingdom and France in the late 1980s; reports in New York City hospitals were soon to follow.¹¹ In the United States, there was a steady increase in the prevalence of VRE during the 1990's in both ICU and non-ICU settings.¹³ VRE currently is more prevalent in the United States than in any other country. A multinational surveillance study conducted during 1997 documented VRE in 14.1% of US isolates, 1.3% of Canadian isolates, and none of the isolates from Latin America.² The overall prevalence of VRE in Europe⁴³ and the Western Pacific⁴⁴ remains low but is on the rise.

The greatest risk factor for the development of VRE infection appears to be prior antimicrobial therapy, especially third-generation cephalosporins and vancomycin.¹¹ The epidemiology of VRE in the United States is very different from that in Europe. It has been speculated that indiscriminate use of vancomycin is at least partially responsible for the emergence of VRE. However, other modifiable factors, such as European use of glycopeptide antibiotics in animal feed, are likely to have contributed as well.¹¹ This theory may be supported by documented VRE colonisation in the faecal flora of healthy patients with no history of hospitalisation or prior glycopeptide therapy.¹¹ Prior cephalosporin or antianaerobic therapy also has been associated with VRE colonisation.⁴⁵⁻⁴⁷ Patient-specific risk factors for nosocomial VRE infection include prolonged hospitalisation and severe underlying disease (e.g. malignancy, solid organ transplantation).^{45,46,48-50}

As with MRSA infections, VRE infections appear to have a negative impact on patient outcomes.⁵¹ A review of 6 studies that stratified patients based on vancomycin sensitivity concluded that VRE infection was consistently associated with higher mortality rates than vancomycin-susceptible enterococcal (VSE) infection.⁵² Mortality rates ranged from 33% to 69% among patients infected with VRE versus 7% to 47% for those with VSE.⁵² In addition, VRE infection has been associated with an increase in the frequency and severity of clinical sequelae.^{51,53} For example, one study revealed that VRE-infected patients were significantly more likely to have recurrent bacteraemia and infection at the primary site.⁵³ The cost of treating patients with VRE is significantly higher than that of susceptible enterococci and may exceed \$80,000 per episode.⁵¹

Minimising Antimicrobial Resistance

Conventional strategies to minimise the development and dissemination of antimicrobial resistance should continue to be encouraged and implemented. These strategies include infection control programmes that promote strict adherence to hand washing and glove use, patient isolation, continuous educational efforts, and local surveillance programmes.⁵⁴⁻⁶⁰ Approximately one third of nosocomial infections are thought to be preventable with simple adherence to infection control measures,⁶¹ and another 32% may be preventable through aggressive infection surveillance.^{58,62} Local surveillance systems provide a keen insight into nosocomial infection rates, causative pathogens, and antimicrobial resistance patterns within an institution. Further, the quality of a hospital's infection control/surveillance programme appears to be the strongest predictor of the level of antimicrobial resistance within an institution.⁵⁷

Secondly, widespread use of antimicrobial agents in hospitals and community-based practices is thought to be a driving force in the development of antimicrobial resistance.⁶⁰ Suggested strategies that appear to minimise antimicrobial resistance focus on optimal use of antimicrobial agents and include (1) infectious disease specialist approval for use of certain antibiotics, (2) use of a restricted antimicrobial formulary, (3) use of automatic stop orders or antibiotic order forms, and (4) use of antimicrobial rotation/cycling.^{63,64} Restrictive formularies are useful for curtailing the use of broad-spectrum antimicrobial drugs, but they may lead to overuse of a small subset of approved drugs.⁶³ Antibiotic order forms are useful for improving physician prescribing, evaluating antimicrobial use, and ensuring that antimicrobial agents are not inappropriately continued.^{61,65} The use of antibiotic rotating or cycling, which use a specific antimicrobial agent only for a prespecified time (which can range from

months to years) has the potential to preserve its long-term therapeutic value; however, prospective studies have not yet been conducted in patients with Gram-positive infections to establish the clinical benefits of this controversial strategy. The combination of infection control and improved antimicrobial use patterns has the potential to limit or reduce the prevalence of multidrug-resistant nosocomial infections.

New Prospects for Management of MRSA and VRE Infections

Until recently, vancomycin was the only therapeutic option for serious MRSA infection. Its use in clinical practice has escalated in response to β -lactam resistance despite concerns of perpetuating the emergence of VRE.¹¹ During the 1990s, the extensive use of vancomycin as surgical prophylaxis and as empiric antimicrobial therapy prompted development of strict guidelines for its use.⁶⁶ Initiation of vancomycin generally is appropriate when there is evidence of (1) serious infections caused by β -lactam resistant Gram-positive organisms, (2) anaphylactoid reactions to β -lactams, (3) MRSA infection, or (4) life-threatening *Clostridium difficile* infection.⁶⁶ In critical care settings, particularly in institutions with a high prevalence of MRSA, using vancomycin as a component of empiric therapy may also be justified. However, if microbiologic findings fail to identify MRSA, vancomycin should be promptly discontinued even in patients experiencing clinical improvement.^{11,66} Treatment of infections due to VRE has been even more problematic because, until recently, there were no antimicrobial agents that were uniformly active against this pathogen.

Linezolid

Overview

Linezolid is the first member of the oxazolidinone class to be approved by the US Food and Drug Administration.¹⁴ Oxazolidinones are chemically unrelated to currently available agents and exert their antimicrobial activity by inhibiting bacterial protein synthesis.⁶⁷ Linezolid selectively binds to the 50S ribosomal subunit, thereby preventing the formation of the functional initiation complex.⁶⁷ This is a novel mechanism of action that appears to result in a lack of cross resistance with other antimicrobial agents.^{18,68,69} Additionally, resistance to linezolid is extremely difficult to select for in vitro.⁷⁰ In the United States, linezolid is commercially available in both oral (tablet and suspension) and intravenous formulations. Oral linezolid is well absorbed from the gastrointestinal tract, with nearly 100% bioavailability and attainment of clinically relevant peak plasma concentrations ($\sim 18 \mu\text{g/mL}$) within 1 to 2 hours.⁶⁸ Dosage adjustments are not required in patients with renal or hepatic insufficiency.

Linezolid has a broad spectrum of activity against Gram-positive organisms in vitro, including susceptible strains of staphylococci, streptococci, and enterococci and resistant strains such as MRSA, VRE, and heterogeneous vancomycin-intermediate *S. aureus*.^{16,19,20,70-73} Preliminary findings of the North American component of the international Zyvox Antimicrobial Potency Study (ZAPS) indicate that linezolid was the only agent with universal in vitro activity against staphylococci, streptococci, and enterococci, including both susceptible and resistant strains.⁷⁴ An in vitro study conducted at Northwestern University from April 1997 through July 2000 found that linezolid was the most active agent against MRSA as well as vancomycin-resistant *E. faecalis* and *E. faecium* (the

comparator agents were vancomycin, quinupristin/dalfopristin, levofloxacin, and moxifloxacin).⁷⁵ In a series of phase III registration studies, linezolid was as effective as comparator agents in treating patients with nosocomial pneumonia, community-acquired pneumonia, and skin and soft tissue infections (Table I).⁷⁶⁻⁸⁰ Of note, linezolid currently is the only antimicrobial agent that is effective against both MRSA and VRE and available in both oral and intravenous formulations.

Linezolid appears to have a favourable adverse event profile.^{68,76,78,83} In clinical trials, the most common adverse events were consistent with most other antimicrobial agents—namely mild to moderate diarrhoea, nausea, and headache that did not require study discontinuation. The

TABLE I: PHASE III CLINICAL TRIALS OF LINEZOLID

Study	Treatment duration	Linezolid regimen	Comparator regimen
Skin/Soft tissue infections (SSTI)			
Complicated SSTI ⁷⁶ -Randomised -Double-blind -Double-dummy -Multicentre	10 to 21 days	Linezolid 600 mg IV every 12 hours If improving—permitted to switch to oral linezolid 600 mg every 12 hours	Oxacillin 2 g IV every 6 hours If improving—permitted to switch to oral dicloxacillin 600 mg every 6 hours
Uncomplicated SSTI ⁷⁷ -Randomised -Double-blind -Multicentre	7 to 14 days	Linezolid 400 mg orally every 12 hours	Clarithromycin 250 mg orally every 12 hours
Pneumonia			
Nosocomial pneumonia ⁷⁸ -Randomised -Double-blind -Multicentre	7 to 21 days	Linezolid 600 mg IV every 12 hours	Vancomycin 1 g IV every 12 hours
Outpatient community-acquired pneumonia ⁷⁹ -Randomised -Investigator-blind -Multinational	10 to 14 days	Linezolid 600 mg orally every 12 hours	Cefpodoxime proxetil 200 mg orally every 12 hours
Hospitalised community-acquired pneumonia ⁸⁰ -Randomised -Open-label -Multinational	7 to 14 days	Linezolid 600 mg IV every 12 hours If improving after one IV dose—permitted to switch to linezolid 600 mg orally every 12 hours	Ceftriaxone 1 g IV every 12 hours If improving after one IV dose—permitted to switch to cefpodoxime 200 mg orally every 12 hours
Resistant infections			
VRE infection ⁸¹ -Randomised -Open-label -Dose-comparative -Multinational	7 to 28 days	Linezolid 600 mg IV or orally every 12 hours or Linezolid 200 mg IV or orally every 12 hours	—
MRSA infection ⁸² -Randomised -Open-label	7-28 days	Linezolid 600 mg IV every 12 hours If improving after 72 hours—switch to oral linezolid 600 mg every 12 hours	Vancomycin 1 g IV every 12 hours

IV: intravenously; MRSA: methicillin-resistant *S. aureus*; VRE: vancomycin-resistant enterococci

rates of these adverse events were similar between linezolid and the comparator agents used in phase III studies.^{68,76,78,83} Reversible thrombocytopenia and anaemia have been reported in a small percentage of patients.¹⁴ Thrombocytopenia generally occurred in patients who received linezolid therapy for longer than 14 days; thus, platelet counts should be monitored in patients receiving prolonged therapy or who have pre-existing risk factors for thrombocytopenia or bleeding.¹⁴ Preclinical studies found that linezolid is a reversible, weak inhibitor of monoamine oxidase. However, no clinically relevant drug-drug interactions have been noted to date, even in patients receiving adrenergic or serotonergic agents.^{76,78,84}

Clinical efficacy of linezolid in MRSA and VRE infections

MRSA infection: The efficacy of linezolid (600 mg intravenously every 12 hours) in the management of hospitalised patients with MRSA infections was compared to that of vancomycin (1 gram intravenously every 12 hours) in a randomised, open-label, multinational study.⁸² Linezolid-treated patients who clinically improved after 72 hours were permitted to receive oral linezolid for the remainder of the study period. Gram-negative coverage with gentamicin was permitted. The planned duration of therapy was 7 to 28 days for both groups.

Preliminary findings of this study were presented at the 9th International Congress on Infectious Diseases (ICID).⁸² The mean durations of therapy were 15.4 days for the linezolid group (mean duration of oral therapy was 6.8 days) and 13.8 days for the vancomycin group. Clinical cure rates among microbiologically evaluable patients were reported as follows: pneumonia—75% for both groups; skin and soft tissue infection—79% for linezolid vs 73% for vancomycin; and other MRSA infection—50% for linezolid vs 67% for vancomycin. None of the differences between the two groups were statistically significant. Thus, linezolid appears to be as effective as vancomycin in hospitalised patients with MRSA infection and allows patients to be switched to oral therapy. Pharmacoeconomic analyses suggest that linezolid has the potential to reduce the overall length of stay (LOS), promote early discharge, and shorten duration of intravenous therapy compared with vancomycin, and may also reduce LOS potentially attributable to infection in patients with methicillin-resistant staphylococcal infections.^{85,86}

A subgroup analysis of this study that only included those patients with complicated skin and soft tissue infections was presented at the 2000 Annual Meeting of the Infectious Diseases Society of America (IDSA).⁸⁸ The treatment regimens were the same as those for the overall study except that the duration of treatment for these patients

was 15 to 21 days. Exclusion criteria included evidence of diabetic foot ulcers or osteomyelitis. The most common baseline diagnoses were surgical wound infection, cellulitis, and ulceration. Clinical cure was achieved by 64% (33/52) and 55% (28/51) of patients who received linezolid and vancomycin, respectively. The microbiological success rates for patients confirmed to have MRSA infection were 79% (27/34) for linezolid and 73% (22/30) for vancomycin. Overall, linezolid appears to be as effective as vancomycin in patients with documented MRSA infection.^{81,88}

VRE infection: Phase III Experience. In a randomised, double-blind, multicentre, phase III study conducted in North America, patients with documented or suspected VRE infections were randomised to receive linezolid 200 mg or 600 mg (intravenously or orally) every 12 hours for a duration of 7 to 28 days.⁸¹ The reason for the dose-comparative design of this study is that no consistently effective comparator was commercially available at the time of study initiation. The protocol permitted concomitant treatment with either an aminoglycoside or aztreonam if there was a concern of a concomitant Gram-negative infection. Inclusion criteria included signs/symptoms of active VRE infection and VRE-positive culture within 96 hours prior to enrollment.

The preliminary results of this study were presented at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC).⁸¹ A total of 145 patients were enrolled into this study, and the most common sites of infection were the urinary tract, skin and soft tissue, and bloodstream. The microbiological cure rate among clinically evaluable patients who received linezolid 600 mg every 12 hours was 88% (37/42), excluding those with missing and indeterminate outcomes. The corresponding success rate in those who received linezolid 200 mg every 12 hours was 62% (23/37) ($P = 0.007$). The microbiologic success rate also was higher in the 600-mg group: 86% (30/35) versus 59% (17/29) for the 200-mg group ($P = 0.0146$). A subsequent analysis according to severity of illness, determined by the Mortality Probability Model II (MPM II), suggests that linezolid 600 mg every 12 hours maintains its effectiveness across all levels of illness severity.⁸⁷

Compassionate-use experience. A substantial number of seriously ill patients have been treated with linezolid on a compassionate-use basis. At Northwestern Memorial Hospital, 7 immunocompromised patients received linezolid for the treatment of a potentially life-threatening VRE infection that could not be treated with other agents (due to intolerance or therapeutic failure).⁸⁹ These patients had acute myelogenous leukaemia ($n = 4$) or non-Hodgkin's lymphoma ($n = 1$), recently received a kidney-pancreas transplant ($n = 1$), or were awaiting liver transplantation ($n = 1$). Linezolid 600 mg every 12 hours was administered

orally or intravenously for 5 to 21 days. One patient who experienced a VRE relapse 64 days after receiving a full course of linezolid was re-treated with a second course.

Our experience with these 7 patients (8 infections) was presented at the 1999 Annual Meeting of the IDSA.⁸⁹ The mean duration of therapy was 12.7 days. Concomitant amikacin or gentamicin was used in the treatment of most (6/8) of the infections. The clinical and microbiological cure rates were 75% (6/8) and 88% (7/8), respectively. An encouraging observation was the eradication of VRE bacteraemia in 4 of the 5 patients (80%) who were neutropenic at infection onset. The only reported adverse events during the study period were oral candidiasis (n = 1) and fungal peritonitis (n = 1). Linezolid was an effective and well-tolerated therapy for VRE infections in this immunocompromised population; larger-scale studies in patients with malignancies are planned.

Linezolid may be effective in the treatment of other serious infections, including endocarditis and osteomyelitis, where bactericidal activity is thought to be mandatory. In vivo models of methicillin-susceptible *S. aureus* (MSSA), MRSA, and vancomycin-resistant *E. faecium* endocarditis suggest that linezolid is more active than vancomycin in reducing bacterial vegetation counts.⁹⁰⁻⁹² In addition, several unpublished cases of endocarditis have been successfully treated with linezolid in the compassionate-use programme. An in vivo study of *S. aureus* osteomyelitis suggested that linezolid was no more active than control and less active than cefazolin; however, animals were treated for only 21 days and linezolid was administered intraperitoneally versus intramuscularly for cefazolin.⁹³ Additional clinical studies evaluating the use of linezolid in patients with osteomyelitis are ongoing. Until further studies/evaluations in these difficult-to-treat infections are complete, the role of an agent, such as linezolid, that is bacteriostatic in vitro against enterococci and staphylococci is unclear.

Quinupristin/Dalfopristin

Overview

Quinupristin and dalfopristin are both bacterial protein synthesis inhibitors that belong to the macrolide-lincosamide-streptogramin class of antimicrobial agents. The combination of quinupristin/dalfopristin produces synergistic in vitro activity (compared to that of either component alone) against susceptible bacteria.⁹⁴ This synergy appears to be the result of a sequential ribosomal binding process: dalfopristin, a group A streptogramin, binds to the ribosome first and induces a conformational change, a process that subsequently enhances the binding ability of quinupristin, a group B streptogramin.⁹⁴ The

principal active metabolite of dalfopristin (pristinamycin IIa) also contributes to the overall antimicrobial activity of quinupristin/dalfopristin—the first commercially available injectable streptogramin. Dosage adjustments are not required for patients with renal dysfunction but, based on available pharmacokinetic data, should be considered in patients with hepatic cirrhosis (no specific recommendations in the US product labelling as of November 2000).^{15,95}

The Gram-positive microbiologic spectrum of quinupristin/dalfopristin includes MRSA and vancomycin-resistant *E. faecium* (VREF).^{17,18,20,21} Importantly, however, it does not include susceptible or resistant strains of *E. faecalis*, necessitating speciation of clinical enterococcal isolates. Quinupristin/dalfopristin was approved in the United States based on its efficacy in (1) a series of comparative phase III studies for complicated skin and soft tissue infections⁹⁶ and (2) a non-comparative phase III study⁹⁷ and emergency-use programme for VRE infections,⁹⁸ which used VRE bloodstream eradication as the surrogate end point for accelerated approval (Table II). Recent clinical studies, as well as surveillance studies, have revealed quinupristin/dalfopristin resistance among clinically important Gram-positive pathogens.^{98,99-102} This relatively rapid emergence of resistance has been partially attributed to prior use of other streptogramins for agricultural purposes and in clinical practice.^{103,104}

Quinupristin/dalfopristin was generally well tolerated in phase III studies and the emergency-use programme.^{96,98} The most problematic adverse events associated with quinupristin/dalfopristin are arthralgias/myalgias and peripheral venous reactions (i.e., inflammation, pain, oedema, and/or phlebitis not relieved by hydrocortisone or diphenhydramine).¹⁰⁵ Administration through a central venous catheter or flushing of peripheral lines following infusion with 5% dextrose in water is recommended to decrease the risk of venous intolerability.^{15,98} Another infusion-related issue with quinupristin/dalfopristin is its incompatibility with heparin and sodium chloride, precluding its co-administration with a number of injectable agents.¹⁰⁵ Of note, Y-site compatibility has been established for selected concentrations of aztreonam, ciprofloxacin, and fluconazole. Quinupristin/dalfopristin is a potent inhibitor of the cytochrome P450 3A4 isoenzyme responsible for the hepatic metabolism of a myriad of therapies, including immunosuppressives (e.g., cyclosporin, tacrolimus), benzodiazepines (e.g., midazolam), and calcium channel blockers (e.g., nifedipine).¹⁵ Therefore, patients on quinupristin/dalfopristin require close monitoring if they are on medications that are metabolised by the cytochrome P450 3A4 isoenzyme.

TABLE II: CLINICAL STUDIES OF QUINUPRISTIN/DALFOPRISTIN FOR COMPLICATED SKIN AND SOFT TISSUE INFECTIONS AND VREF

Study	Treatment duration	Q/D regimen	Comparator regimens
Complicated skin/soft tissue infections			
Phase III international study ⁹⁶ -Open-label -Comparative -Randomised -Multicentre	3 to 14 days	Q/D 7.5 mg/kg IV every 12 hours	Cefazolin 1 g IV every 8 hours or Vancomycin 1 g IV every 12 hours*
Phase III US study ⁹⁶ -Open-label -Comparative -Randomised -Multicentre	3 to 14 days	Q/D 7.5 mg/kg IV every 12 hours	Oxacillin 2 g IV every 6 hours or Vancomycin 1 g IV every 12 hours*
VREF infections			
Phase III study ⁹⁷ -Open-label -Non-comparative -Multicentre	Not specified	Q/D 7.5 mg/kg IV every 8 hours	—
US emergency-use programme (VREF only) ⁹⁸ -Open-label -Non-comparative -Multicentre	Not specified	Q/D 7.5 mg/kg IV every 8 hours	—
Worldwide emergency-use programme (various Gram-positive infections) ⁹⁸ -Open-label -Non-comparative -Multicentre	Not specified	Q/D 7.5 mg/kg IV every 8 hours	—

IV: intravenously; Q/D: quinupristin/dalfopristin; VREF: vancomycin-resistant *Enterococcus faecium*

* Dosages were adjusted according to body weight, renal function, and therapeutic drug levels.

Clinical efficacy of quinupristin/dalfopristin in MRSA and VRE infections

MRSA infection: The therapeutic potential of quinupristin/dalfopristin (7.5 mg/kg intravenously every 8 hours) for MRSA infection was assessed in a multinational study conducted by the Synercid Emergency-Use Study Group.¹⁰⁶ Ninety hospitalised patients had a culture-confirmed MRSA infection, were either intolerant of or failed other regimens, and had no prior history of quinupristin/dalfopristin therapy. Infections of the bone/joint (n = 40) or skin and skin structure (n = 15), endocarditis (n = 11), and respiratory tract infections (n = 10) were the most common diagnoses. The duration of therapy was individualised based on the type and severity of infection and other patient-specific factors (e.g., initial response). Concomitant antimicrobial therapy was permitted; in the subset that was both clinically and microbiologically evaluable (n = 27), the most frequently used agents were ciprofloxacin (n = 10), vancomycin (n = 8), and ceftazidime (n = 6).

The mean duration of therapy was 28.5 days, ranging from 18.2 days for respiratory tract infections to 45.2 days

for bone/joint infections.¹⁰⁶ The clinical cure rates were 76% (68/90) for the enrolled population and 74% (20/27) for the clinically and microbiologically evaluable population. The microbiological success rate in the later group was 67% (18/27). Clinical cure rates among the most common diagnoses ranged from 55% (6/11) for endocarditis to 93% (14/15) for skin and skin structure infections; corresponding rates for those with bone/joint and respiratory tract infection were 78% (31/40) and 70% (7/10), respectively. An encouraging finding was that the macrolide-lincosamide-streptogramin type B constitutively resistant (MLS_{BC}) phenotype, which was identified in approximately 60% of the overall population, did not appear to influence clinical response. Overall, this emergency-use study demonstrated that quinupristin/dalfopristin was a highly effective therapy for numerous types of MRSA infection that could not otherwise be treated.

VRE infection: The Synercid Emergency-Use Study Group simultaneously conducted two open-label studies to prospectively evaluate quinupristin/dalfopristin in the

treatment of VRE infections.⁹⁸ One study was conducted at pre-selected US institutions known to have a high prevalence of VRE, whereas the other was a worldwide study that enrolled patients with in a variety of Gram-positive infections, including VRE. Inclusion criteria included signs of active infection and intolerance or failure to respond to other therapeutic alternatives. A combined total of 396 patients with VRE infection received quinupristin/dalfopristin 7.5 mg/kg intravenously every 8 hours (duration of therapy was based on clinical judgment). The majority of these patients (n = 386) were treated at study sites in the United States. The most common diagnoses were intra-abdominal infection and bacteraemia of unknown origin, accounting for over 60% of the patients. The study population consisted of patients who were seriously ill, as evidenced by a relatively high mean APACHE II score (assessed only in the US study) and multiple co-morbidities.

The published results are based on a combined analysis of both studies.⁹⁸ The mean duration of therapy was 14.5 days. The clinical and microbiological success rates for the enrolled population were 55% (219/396) and 61% (241/396), respectively. The success rates were higher when only evaluable patients were included in the analyses: a 74% (142/193) clinical success rate among clinically evaluable patients and a 71% (110/156) microbiologic success rate among microbiologically evaluable patients. In a subsequent smaller-scale study at UCLA Medical Center, 83% (19/23) of evaluable patients who received quinupristin/dalfopristin 7.5 mg/kg or 5 mg/kg every 8 hours achieved clinical cure or improvement, with a microbiologic cure rate of 74% (17/23).¹⁰² These studies collectively demonstrate that quinupristin/dalfopristin is an effective therapeutic option for the treatment of multidrug-resistant VRE infections.^{98,102}

Investigators at the University of Pittsburgh Medical Center compared the outcomes of 20 liver transplant recipients who received quinupristin/dalfopristin for emergency use with those of a well-matched 42-patient control group.¹⁰⁷ The overall mortality rates were high in both the quinupristin/dalfopristin and control groups (65% and 52%, respectively). However, quinupristin/dalfopristin was associated with a significantly lower rate of VRE-associated mortality (25% versus 40% for the control group, respectively; $P = 0.05$), as well as fewer cases of recurrent bacteraemia and persistence of VRE at the primary infection site.

When to Use Linezolid Versus Quinupristin/Dalfopristin

These newer antibiotic agents should be used appropriately based on the specific suspected or documented infection and patient-specific factors. Reserving use of

these agents until all other therapies have failed may deny patients life-saving treatments.¹⁰⁸ Linezolid has the potential for wider use over quinupristin/dalfopristin for several reasons. Linezolid does not require central line drug administration and it is available in a 100% bioavailable oral dosage form making dosing interchange a simple 1:1 conversion.¹⁴ Intravenous to oral continuation therapy with linezolid in clinically stable patients may reduce the hospital LOS and facilitate early discharge, as shown in patients with methicillin-resistant staphylococcal infections.⁸⁶ Patients with previous exposure to multiple antibiotics, including vancomycin or quinupristin/dalfopristin, or those with previously known resistant infections may be suitable candidates for linezolid. Linezolid does not require dosage adjustment for patients with unstable renal or mild to moderate hepatic function, and because linezolid does not interact with the hepatic P450 system, it may be the preferred agent in critically ill patients with suspected or documented MRSA or VRE infections.

Quinupristin/dalfopristin is available only in intravenous form that requires central venous drug administration. Dosage adjustments are not required for renal impairment but may be necessary in patients with hepatic cirrhosis. Quinupristin/dalfopristin does significantly inhibit cytochrome P450 3A4 and may interact with agents sharing that metabolic route.¹⁵ It appears this streptogramin is most widely used for patients in specialist units with vancomycin-resistant *E. faecium* infections.¹⁰⁸ Until further studies in special populations (immunocompromised, endocarditis, osteomyelitis) are available, comment on the use of either agent should be reserved.

Prudent and careful use of these agents in patients with highly suspect or documented resistant Gram-positive infections is recommended. If susceptibility testing fails to prove a Gram-positive aetiology of a suspected infection in a patient empirically treated with linezolid or quinupristin/dalfopristin, then these agents (as well as vancomycin) should not be continued. Drug cost is likely to limit overuse of these agents. Quinupristin/dalfopristin is three times more expensive than linezolid, and both are more expensive than vancomycin. However, if one considers the total cost of therapy (LOS due to intravenous therapy, monitoring, costs of outpatient intravenous treatment) including potential complications (treatment failure, adverse events, nephrotoxicity, and refractory, nosocomial, or catheter-related infections), vancomycin may ultimately be more costly compared with the newer agents.¹⁰⁹ Individual institutions should base their decisions regarding access to these agents on the levels of antibiotic resistance and types of patient populations most often requiring Gram-positive treatment in their individual institutions.

Conclusions

The socioeconomic impact of multidrug-resistant Gram-positive infections clearly is substantial. VRE has emerged as an important nosocomial pathogen in the United States. Furthermore, vancomycin resistance appears to be slowly evolving among MRSA strains. Continued adherence to infection control programmes and optimal antimicrobial use may substantially reduce the emergence of resistant Gram-positive pathogens. The recent introductions of linezolid and quinupristin/dalfopristin in the United States and abroad provide clinicians with new options for treating MRSA, VRE, and other Gram-positive infections. Quinupristin/dalfopristin provides effective treatment for eradicating VRE, a common cause of infection in patients with severe underlying comorbidities; however, its utility may be limited by toxicities. The availability of linezolid in oral and intravenous formulations has the potential to facilitate step-down treatment for Gram-positive infections and faster hospital discharge.

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