

Clinical update on linezolid in the treatment of Gram-positive bacterial infections

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Abstract: Gram-positive pathogens are a significant cause of morbidity and mortality in both community and health care settings. Glycopeptides have traditionally been the antibiotics of choice for multiresistant Gram-positive pathogens but there are problems with their use, including the emergence of glycopeptide-resistant strains, tissue penetration, and achieving and monitoring adequate serum levels. Newer antibiotics such as linezolid, a synthetic oxazolidinone, are available for the treatment of resistant Gram-positive bacteria. Linezolid is active against a wide range of Gram-positive bacteria and has been generally available for the treatment of Gram-positive infections since 2000. There are potential problems with linezolid use, including its bacteriostatic action and the relatively high incidence of reported adverse effects, particularly with long-term use. Long-term use may also be complicated by the development of resistance. However, linezolid has been shown to be clinically useful in the treatment of several serious infections where traditionally bacteriocidal agents have been required and many of its adverse effects are reversible on cessation. It has also been shown to be a cost-effective treatment option in several studies, with its high oral bioavailability allowing an early change from intravenous to oral formulations with consequent earlier patient discharge and lower inpatient costs.

Keywords: linezolid, oxazolidinone, multi-resistant, gram-positive, MRSA, VRE, cost-benefit

Introduction to the management of Gram-positive bacterial infections

Gram-positive pathogens, including *Staphylococcus aureus*, enterococci, and *Streptococcus pneumoniae*, cause significant morbidity and mortality in the community and hospital settings. Infections due to multidrug-resistant Gram-positive bacteria are increasing in prevalence, with an increase in the incidence of virulent clones of community-acquired methicillin-resistant *S. aureus* (MRSA), multidrug-resistant *S. pneumoniae*, and enterococci species which are increasingly resistant to multiple antimicrobial agents in many parts of the world. The traditional antibiotic of choice for these multiresistant pathogens has been vancomycin but there is an increase in treatment failure as vancomycin-resistant strains have emerged. Glycopeptide treatment also has inherent problems with drug penetration into tissues and the need to monitor and achieve adequate serum levels. Newer antibiotics available for use against resistant Gram-positive bacteria include linezolid, daptomycin, quinupristin/dalfopristin, tigecycline, and semisynthetic lipoglycopeptides, such as telavancin. Cephalosporins and carbapenems with MRSA activity are also being developed.

Linezolid was the first oxazolidinone developed. It was approved for clinical use in the US in April 2000 and in the UK in January 2001. Its licensed indications include

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community-acquired and nosocomial pneumonia and skin and soft tissue infections. It is licensed for pediatric use in the US but not in the UK.

Microbiological activity

Linezolid is active against a wide-range of Gram-positive aerobic bacteria¹ and some Gram-positive anaerobes, including *Actinomyces* spp. It is also active against some Gram-negative anaerobic bacteria, several Mycobacterial species and against *Nocardia* spp.

Gram-positive aerobic bacteria

Linezolid has good activity against many Gram-positive aerobic bacteria, including resistant strains of several species, such as MRSA, penicillin-resistant pneumococci (PRP), and vancomycin-resistant enterococci (VRE).

Minimum inhibitory concentrations (MICs) of coagulase-negative staphylococci (CoNS) are generally lower to linezolid than those of *S. aureus* spp.² MICs to linezolid of both CoNS and *S. aureus* are not altered by whether the strains are methicillin-susceptible or resistant:³ decreased susceptibility of staphylococcal species to vancomycin is not associated with decreased susceptibility to linezolid.⁴

Linezolid is active against many streptococci, including group A, B, C, F, and G β -hemolytic streptococci, viridians streptococci, and enterococci.^{5–7} Most streptococci have MICs ranging up to 2 mcg/mL, although some group A streptococci and some strains of viridians streptococci have been found to have MICs up to 4 mcg/mL.⁸ PRP remain susceptible to linezolid.⁹ Vancomycin-susceptible enterococci and VRE have similar MICs to linezolid.^{2,3} *Corynebacterium* spp., *Listeria monocytogenes*, *Bacillus* spp., *Rhodococcus equi*, *Nocardia* spp., and many *Lactobacillus* spp. are susceptible to linezolid.^{6,10–13}

Anaerobic bacteria

Several Gram-positive and Gram-negative anaerobic bacteria are susceptible to linezolid, including many strains of *Clostridium difficile*,^{14,15} *Fusobacterium* spp.,¹⁶ *Prevotella* spp.,¹⁷ and *Bacteroides* spp.¹⁸ Linezolid is active against some strains of *Actinomyces* spp.¹⁹

Mycobacteria

Linezolid is active against *Mycobacterium tuberculosis* and several atypical mycobacteria. In general, the slow-growing mycobacteria are susceptible to linezolid, although some, such as *M. avium* Complex (MAC), are usually resistant.²⁰

Rapidly growing atypical mycobacteria are less susceptible and MICs need to be determined.²¹

Mode of action

Linezolid inhibits protein synthesis by binding to domain V of the 23S ribosomal RNA (rRNA) of the 50S subunit of bacterial ribosomes;²² it has been shown to bind to the peptidyltransferase center (PTC) of the bacterial ribosome.^{23,24}

Resistance to linezolid

Resistance rates to linezolid are low.^{25,26} Linezolid resistance occurred in <1% of *S. aureus*, CoNS, and enterococci isolates from the US between 2002 and 2009.²⁷ Linezolid resistance in clinical isolates was first reported in *Enterococcus faecium*^{28,29} and in *S. aureus*³⁰ and has since been reported in CoNS, *Enterococcus faecalis*, and viridians streptococci.^{31–33} Resistance occurs most often due to point mutations in the 23S rRNA drug target site.³⁴ Mutations of 23S have been reported in resistant *S. aureus*,³⁴ CoNS,³⁵ and enterococci.^{29,34} The most frequent of these mutations is G2576T.^{36,37} Resistance usually develops after prolonged therapy with linezolid for serious infection,³⁸ although nosocomial acquisition of both resistant enterococci³⁹ and CoNS³⁵ has been reported, including cases in patients with no prior treatment with linezolid.³⁹ Resistance develops slowly, because nearly all bacteria possess multiple copies of the 23S rRNA gene.³⁶ It has been proposed that combination with a second antibacterial agent, particularly rifampicin or fusidic acid, may delay the emergence of linezolid resistance in *S. aureus*.⁴⁰ More recently, linezolid resistance has been identified due to acquisition of a natural resistance gene, *cfr* (chloramphenicol-florfenicol resistance). The product of the *cfr* gene is a methyltransferase that catalyzes methylation of A2503 in the 23S rRNA gene of the large 50S ribosomal subunit, conferring resistance to chloramphenicol, florfenicol, and clindamycin.⁴¹ The first *cfr*-mediated, linezolid-resistant clinical isolate of MRSA was reported in 2007.⁴²

Pharmacokinetics

Absorption and bioavailability

Linezolid is rapidly absorbed orally, with almost 100% bioavailability⁴³ so that oral and intravenous (iv) doses are equivalent and no dose adjustment is needed when switching between the two routes of administration. Peak levels (C_{max}) are reached 1–2 hours after an oral dose.^{44,45} Taking linezolid with high-fat food will decrease C_{max} by approximately 20% and prolong the time taken to reach C_{max} by about 1–2 hours⁴³

but will not affect the area under the serum concentration–time curve (AUC).⁴⁶

The oral absorption of linezolid is not affected by the co-administration of antacids.⁴⁷

A recent study in eight adult cystic fibrosis (CF) patients showed bioavailability to be reduced to approximately 85% in this patient group,⁴⁸ possibly due to pancreatic enzyme deficiency.

The pharmacokinetics of linezolid are largely linear, with the C_{max} and AUC being proportional to the dose over the therapeutic dose range; there is a slight amount of nonlinearity at high-dose ranges, where a decrease in clearance is observed.⁴⁶ The pharmacokinetic/pharmacodynamic parameters that are most predictive of efficacy for linezolid are the time above MIC ($T > MIC$) and the ratio of the AUC to the MIC (AUC/MIC).⁴⁶

Serum concentrations are above the MIC_{90} for susceptible pathogens for most of the dosing interval when given 12-hourly.⁴⁹ However, linezolid levels have been found to be variable^{50,51} and may be suboptimal in some patient populations.⁵² Plasma linezolid concentrations in elderly patients, patients with mild-to-moderate hepatic impairment or mild to severe renal impairment are similar to those achieved in young or healthy volunteers.^{46,53}

Distribution and tissue penetration

Linezolid is approximately 31% protein bound⁵⁴ which is not concentration dependent. The volume of distribution is approximately 40–50 L, ie, approximately total body water content.⁵⁰

Skin, fat, and musculoskeletal tissues

There is good penetration of linezolid into skin blister fluid⁴⁴ indicating good tissue penetration. High linezolid levels have been demonstrated in adipose tissue and skeletal muscle.⁵⁵ Other studies have shown that linezolid penetrates well into bone, muscle, and tissues surrounding infected prosthetic joints.^{56,57}

Respiratory tissues

Linezolid has been shown to penetrate well into lung epithelial lining fluid of patients with ventilator-associated pneumonia (VAP),⁵⁸ those undergoing diagnostic bronchoscopy,⁵⁹ and healthy volunteers.⁶⁰ The study by Conte et al⁶⁰ showed much less penetration into alveolar cell fluid.

Central nervous system

Linezolid penetration into cerebrospinal fluid (CSF) has been investigated in several studies. Tsona et al looked at

CSF levels after a single iv dose of 600 mg linezolid in 18 patients undergoing neurosurgery.⁶¹ Mean concentrations of linezolid in serum, CSF, and brain tissue were assayed by high-performance liquid chromatography (HPLC); CSF/serum and brain/serum ratios were 69.57% and 44.66%, respectively. Concentrations of linezolid were above the MIC_{90} for staphylococci and for streptococci. Boak et al also reported good penetration of linezolid into CSF in a patient with CoNS ventriculitis⁶² and Myrianthefs et al reported good linezolid concentrations in the CSF of patients receiving linezolid for treatment or prophylaxis of CNS infections.⁶³ Beer et al measured linezolid levels in the serum and CSF of five patients with extraventricular devices (EVDs) and staphylococcal ventriculitis receiving linezolid 600 mg twice daily iv.⁶⁴ The mean CSF:plasma ratio was 0.8 ± 0.3 . Times above the MIC in CSF were 99.8% and 57.2% for pathogens with MICs of 2 mg/L and 4 mg/L, respectively. However, Viaggi et al measured plasma and CSF linezolid concentrations by HPLC after the 1st and 5th dose of linezolid in seven patients with external ventricular drainage, who received linezolid 600 mg iv infusions twice daily to prevent CNS infections.⁶⁵ CSF AUC (range 18.2–85.5 and 19.6–160.5 h \times mg/L at the 1st and 5th dose, respectively) were lower than those calculated in plasma (range 27.6–224.0 and 27.5–166.1 h \times mg/L, respectively). For $MIC = 1$ mg/L, CSF AUC/MIC values were nearly equal to or greater than 100 only in two subjects after the 1st and 5th dose, whereas $T > MIC$ values were higher than 75% in only three patients.

Eyes

Linezolid has been shown to reach good levels in the aqueous humor of patients after a single oral or iv 600 mg dose prior to routine cataract surgery.^{66,67}

Other tissues

Linezolid has also been shown to have good penetration into the interstitial fluid of critically ill patients,⁶⁸ the pancreatic fluid of patients with pancreatic abscesses,⁶⁹ and the peritoneal dialysis fluid of a patient with peritonitis.⁷⁰ Dehghanyar et al showed that linezolid in the tissues of healthy volunteers reached concentrations sufficient to inhibit the growth of pathogens with MICs up to 4 mg/L, including MRSA and VRE, throughout the dose interval, although they also observed large variations in tissue linezolid concentrations between individuals, suggesting that in some individuals, some pathogens with MICs of 2 mg/L or higher would not be optimally inhibited.⁷¹

Breast milk

Linezolid can be detected in breast milk after oral administration.⁷²

Biofilms

Treatment of biofilm-associated infections is a major problem associated with medical implants. Several studies have attempted to look at the role of linezolid in the treatment of biofilm-associated infections. Wilcox et al looked at biofilm concentrations of linezolid and of vancomycin in Gram-positive catheter-associated biofilms after perfusion of the catheter lumens with antibiotics;⁷³ they found vancomycin concentrations were generally greater than linezolid concentrations after a single exposure but neither antibiotic achieved consistent 100% kill of biofilm bacteria after single infusions, even when a very high concentration was present.

Wiederhold et al looked at the antibiotic activity of linezolid and vancomycin in vitro against Gram-positive bacteria in catheter-associated biofilms and found neither completely eradicated bacterial colonization of the catheters. Both linezolid and vancomycin suppressed bacterial growth of *S. aureus* and *S. epidermidis* compared with controls, while linezolid also suppressed counts compared with control and vancomycin versus VRE.⁷⁴

Bayston et al investigated the effect of penicillin G, linezolid, and rifampicin on *Propionibacterium acnes* in biofilms.⁷⁵ They demonstrated 14 days' treatment with penicillin G, linezolid, or linezolid/rifampicin combination eradicated the growth of *P. acnes* whereas only penicillin G had this effect after just 7 days' treatment. After 9 days' re-incubation, the biofilms were re-cultured to detect "relapse"; penicillin G and linezolid/rifampicin showed no relapse but linezolid alone showed relapse growth at 14 days ($P < 0.001$).

Leite et al studied the susceptibility of *S. epidermidis* in biofilms to daptomycin, linezolid, and rifampicin in vitro by measuring colony-forming unit (CFU) reductions at MIC and peak serum concentrations.⁷⁶ There was less CFU reduction with linezolid than with the other two antibiotics at peak serum concentrations and MICs.

Bayston et al looked at the actions of linezolid or vancomycin on biofilms of MRSA, MRSE, *E. faecalis*, and *E. faecium* on ventriculoperitoneal shunts.⁷⁷ They found both linezolid and vancomycin caused eradication of staphylococci after 14 days of treatment at concentrations achievable in CSF and prevented its re-growth in the next 14 days, whereas neither antibiotic led to eradication or prevented re-growth of enterococci. Holmberg et al assessed the in vitro susceptibility of four isolates of *E. faecalis* from prosthetic

knee and hip joints.⁷⁸ The minimum bacterial eradication concentrations (MBECs) were determined for ampicillin, vancomycin, linezolid, ciprofloxacin, and rifampicin, alone and in combinations, and were found to be reduced for linezolid and for ciprofloxacin if combined with rifampicin, compared with uncombined treatment. The combination of ciprofloxacin and rifampicin was most effective at reducing bacterial growth, measured as CFU after 8 hours' exposure of the biofilm to the antibiotic(s), followed by the linezolid/rifampicin combination. Sandoe et al looked at the antibiotic activity of linezolid, ampicillin, and vancomycin against 58 enterococcal isolates from biofilms and found the majority demonstrated tolerance (defined as $MBC/MIC > / = 32$), that very high concentrations of all the antibiotics tested were needed to inhibit enterococcal biofilms in vitro and that the addition of gentamicin to any of the antibiotics only led to a significant reduction in MIC and MBC for some of the isolates.⁷⁹

Excretion

About 30% of linezolid is excreted unchanged in the urine – the remainder undergoes renal and non-renal metabolism; it is oxidized to two main inactive metabolites.⁵⁰ About 55% is excreted in the urine as metabolites and 10% in feces as metabolites.^{45,46} The plasma elimination half-life is 4.5–5.5 hours.⁴⁵

Renal clearance is about 30–50 mL/minute in healthy volunteers, while non-renal clearance varies between 70–150 mL/minute.⁴⁵ No dose adjustment is necessary in renal impairment⁸⁰ or in mild-to-moderate liver impairment.⁸¹ In patients who are undergoing renal dialysis and who are being treated with linezolid, the dose should be given after a dialysis session as 30%–40% is removed by dialysis.⁸² A significant amount of linezolid is also removed by continuous venovenous hemofiltration (CVVH)⁸³ but no dose adjustment is currently recommended.⁸⁴ However, the study of Meyer et al showed that, for pathogens with an MIC up to 4 mg/L, the $T > MIC$ was 57% ($\pm 32\%$) in CVVH patients receiving a standard dosage regimen of 600 mg linezolid twice daily, compared to a $T > MIC$ of 93% for pathogens with an MIC of 2 mg/L, suggesting that some patients with less susceptible pathogens might benefit from an 8-hourly dosing regimen instead of 12-hourly.⁸³

Linezolid clearance is higher in children than in adults, with a greater volume of distribution, shorter half-life, and smaller AUC,⁸⁵ and therefore higher daily dosages are required in children. Clearance declines with age but no further dose adjustment with age is required.⁵⁰

Pharmacodynamics

Linezolid is predominantly bacteriostatic in vitro against staphylococci and enterococci at concentrations of 2–10 times the MIC^{50,86} and at higher concentrations.⁸⁷ Some bactericidal activity has been reported for linezolid against *S. pneumoniae* and *S. pyogenes*.⁸⁸ Bacteriocidal activity has also been reported in a rabbit model of *S. aureus* endocarditis when the linezolid was given as a continuous infusion instead of intermittent doses.

Linezolid has a short post-antibiotic effect against *S. aureus*, enterococci, and *S. pneumoniae*.⁸⁹

Dosage

The approved dose of linezolid in adults is 600 mg orally or intravenously every 12 hours. The dose for children under 12 years old is 10 mg/kg three times daily.⁸⁵

Efficacy studies

See table 1 for summary of efficacy studies.

Bacteremia

Wilcox et al looked at the use of linezolid vs teicoplanin⁹⁰ in a randomized, controlled, open-label, multicenter study of 430 patients with suspected or proven Gram-positive infection. Patients were treated with linezolid or teicoplanin for up to 28 days. Clinical cure rates for the patients with bacteremia were statistically significantly higher between the two treatment arms (88.5% vs 56.7%, $P = 0.009$, 95% confidence interval [CI]: 10.2–53.4). A Phase III study by Wilcox et al compared linezolid with vancomycin treatment of complicated skin and soft-tissue infections (cSSTIs) and catheter-related bloodstream infections in an open-label, multicenter, comparative study.⁹¹ They concluded that microbiological success with linezolid was noninferior to that with vancomycin in patients with cSSTIs and catheter-related bloodstream infections caused by Gram-positive organisms.

A meta-analysis by Falagas et al concluded that treatment with linezolid had significantly better success rates than treatment with comparator drugs in patients with Gram-positive bacteremia (81.3% vs 66.4%).⁹²

A meta-analysis by Beibei et al looked at results from 271 evaluable patients in three RCTs where linezolid was used to treat patients with bacteremia and found no statistically significant difference in treatment success between those receiving linezolid or vancomycin.⁹³

Jang et al compared salvage treatment with linezolid (+/- a carbapenem) to vancomycin (+gentamicin or rifampicin) in a small open-label retrospective study of 35 patients with persistent MRSA bacteremia.⁹⁴ Nineteen patients, including four with positive hetero-Vancomycin-intermediate Staphylococcus

aureus (VISA) screening tests, received vancomycin-based treatment and 16 patients received linezolid-based treatment. The early microbiological response (ie, negative follow-up blood culture within 72 hours) was significantly higher in the linezolid-based salvage therapy group than the vancomycin-based group (75% vs 17%; $P = 0.006$). The salvage success rate was higher for linezolid therapy than for vancomycin-based combination therapy ($P < 0.001$); linezolid-based therapy gave an 88% salvage success rate.

Skin and soft tissue infection (SSTI)

Several randomized clinical trials have been carried out comparing the efficacy of linezolid with comparator drugs for the treatment of SSTI. Jauregui et al compared linezolid 12-hourly for 14 days to dalbavancin once weekly (two doses) for the treatment of SSTI, including infections with MRSA, in 854 patients in a Phase III multicenter, double-blind RCT.⁹⁵ Efficacy was assessed by clinical and microbiological responses. Dalbavancin and linezolid demonstrated comparable clinical efficacy in the clinically evaluable population at the test-of-cure visit (88.9% and 91.2% success, respectively). Weigelt et al compared linezolid to vancomycin in the treatment of 1200 patients with proven or suspected MRSA complicated SSTIs (cSSTIs) in an open-label RCT.⁹⁶ The results showed linezolid was more effective than vancomycin (based on test-of-cure visit) in patients with abscesses and in those with MRSA infections. Wilcox et al compared clinical success at end-of-treatment visit in patients who received linezolid (117 patients) or teicoplanin (111 patients) for the treatment of Gram-positive SSTI, and found no statistical significance between the two groups.⁹⁰ Stevens et al carried out a randomized, double-blind, multicenter trial comparing the efficacy of linezolid with that of oxacillin in 826 patients with complicated SSTIs and found that linezolid was as effective as oxacillin in the treatment of these infections.⁹⁷ A meta-analysis of RCTs by Falagas et al found linezolid was significantly more effective in treating SSTIs than comparators (beta-lactams or glycopeptides) (90.3% vs 85.7% success of treatment).⁹² A meta-analysis of RCTs by Beibei et al concluded that linezolid was more effective treatment than vancomycin in patients with SSTIs (odds ratio [OR]: 1.40, 95% CI: 1.01–1.95).⁹³ Bounthavong and Hsu evaluated the clinical and microbiological outcomes of linezolid compared to vancomycin in MRSA cSSTIs using a meta-analysis of five studies with a total of 2652 patients (1361 linezolid; 1291 vancomycin) and concluded that linezolid was more likely to achieve microbiological eradication of MRSA than vancomycin in these infections.⁹⁸

Table 1 Summary of efficacy studies/reports

Author	Study design/ case details	Antibiotic (linezolid or comparator drugs)	Results/conclusions
Bacteraemia			
Wilcox et al ⁹⁰	RC, OL, MC, 430 pts with GP infections, 56 with bacteremia	Teicoplanin for up to 28 days	Clinical cure rates for bacteremia patients 88.5% (linezolid) vs 56.7% (teicoplanin) $P = 0.009$
Wilcox et al ⁹¹	Phase III, OL, MC Patients with GP cSSTI and CRBSI	Vancomycin	Non-inferiority of linezolid in microbiological success
Jang et al ⁹⁴	Salvage therapy in 35 patients with persistent MRSA bacteremia, OL, retrospective	Linezolid +/- carbapenem vs vancomycin + (gentamicin or rifampicin)	EMR higher in linezolid-treated pts than vancomycin-treated patients (75% vs 17% $P = 0.006$). Salvage success rate in linezolid patients (88%) significantly higher than in vancomycin pts ($P < 0.001$)
Falagas and Vardakas ¹³¹	Meta-analysis: 255 pts in 5 RCTs	β -lactams and glycopeptides	Success rates in GP bacteraemia 81.3% (linezolid) vs 66.4% (comparator)
Beibei et al ⁹³	Meta-analysis: 271 pts in 3 RCTs	Vancomycin	No statistically significant difference in treatment success in bacteremia patients between linezolid and vancomycin
Skin and soft tissue infections			
Jauregui et al ⁹⁵	854 pts, phase III MC, DB, RCT	Dalbavancin	No significant difference in efficacy: 88.9% vs 91.2%
Weigelt et al ⁹⁶	1200 pts OL RCT	Vancomycin	Linezolid more effective than vancomycin in pts with abscesses and those with MRSA
Wilcox et al ⁹⁰	228 pts, GP SSTI	Teicoplanin	No statistical difference
Stevens et al ⁹⁷	826 pts RCT, DB, MC	Oxacillin	Linezolid as effective as oxacillin in treatment of cSSTI
Falagas and Vardakas ¹³¹	Meta-analysis: 2661 pts in 8 RCTs	β -lactams and glycopeptides	Linezolid significantly more effective than comparators 90.3% vs 85.7% success
Beibei et al ⁹³	Meta-analysis: 271 pts in 3 RCTs	Vancomycin	linezolid more effective treatment than vancomycin (OR = 1.40, 95% CI 1.01–1.95)
Bounthavong and Hsu ⁹⁸	Meta-analysis of 5 studies, 2652 pts, MRSA cSSTIs	Vancomycin	Linezolid more likely to achieve microbiological eradication of MRSA than vancomycin in MRSA cSSTI infections
Pneumonia			
San Pedro et al ¹⁰⁰	747 pts with CAP, MC, OL, RCT	Linezolid +/- aztreonam vs ceftriaxone/cefepodoxime	Higher cure rate overall in the linezolid-treated patients (83% vs 76.4% $P = 0.04$) Of 254 patients with <i>S pneumoniae</i> , no significant difference in cure rates; sub-group with <i>S pneumoniae</i> bacteraemia had significantly better cure rate in linezolid arm (93.1% vs 68.2%; $P = 0.021$)
Walkey et al ¹⁰¹	Meta-analysis: 1641 pts in 8 trials	Glycopeptides	Linezolid not superior to glycopeptides for suspected MRSA nosocomial pneumonia.
Falagas and Vardakas ¹³¹	Meta-analysis: 864 pts in 7 RCTs	β -lactams and glycopeptides	No significant difference in outcomes in patients with GP pneumonia or nosocomial pneumonia.
Wunderink et al ¹⁰²	Prospective DB, MC RCT 348 pts with MRSA pneumonia	Vancomycin (dose adjusted as per trough levels)	Linezolid treatment had higher clinical success rates than vancomycin treatment; 95/165 (57.6%) vs 81/174 (46.6%) $P = 0.042$ in evaluable per protocol pts
Bone and joint infections			
Aneziokoro et al ¹⁰⁵	Retrospective in 20 patients	Linezolid for 6 + weeks	55% clinical cure rate in osteomyelitis
Rayner et al ¹⁰⁶	Compassionate use in 22 patients	Linezolid	82% clinical cure rate in osteomyelitis
Endocarditis			
Falagas et al ¹¹²	Systemic review of use in 33 patients	Linezolid +/- other	Linezolid is potentially useful for endocarditis, including after vancomycin failure
CNS			
Zeana et al ¹¹⁸	Case report	Linezolid	VRE
Faella et al ¹¹⁹	Case report	Linezolid	PRP
Ramirez et al ¹²⁰	Case report	Linezolid	PRP after vancomycin failure
Leiti et al ¹²¹	Case report	Linezolid + rifampicin	<i>L monocytogenes</i> brain abscess
Viganò et al ¹²²	Case report	Lineolid	Nocardial brain abscess

(Continued)

Table I (Continued)

Author	Study design/ case details	Antibiotic (linezolid or comparator drugs)	Results/conclusions
Febrile Neutropenia			
Jaksic et al ¹²³	DB RCT	Vancomycin 1g bd 10–28 days	Similar clinical success rates and safety profiles between linezolid and vancomycin groups
Mycobacterial Infections			
Nannini et al ¹²⁴	Case report in patient with CLL	Part of combination treatment including moxifloxacin	Disseminated MAC infection
Kyle and Porter ¹²⁵	Case report	Part of combination treatment with clarythromycin	<i>M chelonae</i> infection
Ntziora and Falagas ¹²⁶	Review of 24 cases	Part of combination treatment	May be beneficial in combination treatment for Mycobacterial infections, including <i>M tuberculosis</i> , but long-term use often limited by drug-related adverse effects.

Abbreviations: MC, multi-centre; RCT, randomized controlled trial; OL, open-label; DB, double-blind; GP, gram positive; cSSTI, complicated skin and soft tissue infection; CRBSI, catheter-related blood stream infection; EMR, early microbiological response; MAC, *M avium* Complex; CLL, chronic lymphocytic leukaemia; CAP, community-acquired pneumonia; PRP, penicillin resistant pneumococcus; VRE, vancomycin resistant enterococcus; MRSA, methicillin resistant *Staphylococcus aureus*; bd, twice daily.

Pneumonia

The efficacy of linezolid in the treatment of both community acquired pneumonia (CAP) and hospital acquired pneumonia (HAP) has been investigated in many trials. It has been shown to penetrate well into the lung epithelial lining fluid of healthy volunteers⁶⁰ and patients with VAP⁵⁸ and into parapneumonic pleural effusions.⁹⁹ San Pedro et al compared linezolid (+/- aztreonam) to iv ceftriaxone followed by oral cefpodoxime for the treatment of CAP, in 747 patients in a multicenter, randomized, open-label trial.¹⁰⁰ There was a higher cure rate overall in the linezolid-treated patients (83% vs 76.4%; $P = 0.04$). However, of the 254 patients with *S. pneumoniae* isolated, there was no significant difference in cure rates between the two arms, except in the subgroup with *S. pneumoniae* bacteremia, where the linezolid-treated group had a superior clinical cure rate (93.1% vs 68.2%; $P = 0.021$).

A meta-analysis of trials by Walkey et al compared treatment with glycopeptides to linezolid for suspected MRSA nosocomial pneumonia, using data from 1641 patients in eight trials and concluded that linezolid was not superior to glycopeptides for these patients.¹⁰¹ A meta-analysis of RCTs by Falagas et al found no significant difference between linezolid or comparator drug in patients with Gram-positive pneumonia or nosocomial pneumonia.⁹²

Wunderink et al carried out a prospective, double-blind, multicenter RCT of adult patients with nosocomial MRSA pneumonia treated with linezolid or with a dose-optimized vancomycin regimen where the vancomycin dose was adjusted on the basis of trough levels.¹⁰² In the evaluable per-protocol patients, 95/165 (57.6%) linezolid-treated patients and 81/174 (46.6%) vancomycin-treated patients achieved clinical success which was statistically significant (95% CI: 0.5%–21.6%; $P = 0.042$).

Bone and joint infections

Linezolid has good penetration into bone and surrounding tissue¹⁰³ and it has been used to treat osteomyelitis, septic arthritis, and prosthetic joint infections due to several microorganisms, including MRSA, CoNS, VRE, and VISA, either alone or in combination.^{69,104} Aneziokoro et al looked retrospectively at the clinical effectiveness of at least 6 weeks of oral linezolid therapy for osteomyelitis.¹⁰⁵ The clinical cure rate was 55% for the 20 patients who received at least 6 weeks of therapy. Rayner et al looked at the results of linezolid treatment of osteomyelitis in patients in a compassionate use program; of 22 patients evaluable, there was an 82% clinical cure rate.¹⁰⁶

Endocarditis

Despite its bacteriostatic rather than bactericidal action, linezolid has been used to treat endocarditis, particularly where multiresistant organisms are involved. Animal experiments have suggested linezolid may be effective at treating MRSA endocarditis if plasma concentrations of linezolid are above the MIC of the organism¹⁰⁷ and that it may be useful in VRE endocarditis.¹⁰⁸ Several case reports of the use of linezolid to treat endocarditis due to resistant organisms have been published, with varying success reported.^{104,109–111} Falagas et al carried out a systematic review of the use of linezolid in the treatment of endocarditis, either as a single agent or in combination with other antibiotics.¹¹² Results from 33 patients were included, most with MRSA or VISA. They concluded that linezolid is potentially useful as a treatment option for endocarditis where other treatments are limited, including cases where vancomycin treatment has failed. A combination of linezolid with gentamicin has been shown to be bactericidal when used in an experimental model of MRSA endocarditis.¹¹³

Central nervous system

There have been several case reports of the successful use of linezolid in the treatment of post-neurosurgical and post-traumatic CNS infections.^{114–116} Linezolid has been shown to have good penetration into the CSF.^{61,117} Linezolid has also been used to treat CNS infections caused by resistant organisms, including by VRE¹¹⁸ and by PRP,¹¹⁹ including treatment of PRP after failure of vancomycin.¹²⁰ There have been case reports of the successful use of linezolid with rifampicin to treat a brain abscess due to *L. monocytogenes*¹²¹ and of its use to successfully treat Nocardial brain abscesses.¹²²

Febrile neutropenia

Jaksic et al compared the clinical outcomes in cancer patients with febrile neutropenia treated with linezolid 600 mg twice daily or with vancomycin 1 g twice daily in a DB RCT;¹²³ clinical success rates 7 days after the completion of therapy were equivalent in the two groups, with similar safety profiles.

Mycobacterial infections

Linezolid has been shown to have in vitro activity against some mycobacteria. There have been case reports of its success use in combination treatments of a disseminated *M. avium* complex infection refractory to first-line treatment¹²⁴ and of a *M. chelonae* infection.¹²⁵ Ntziora and Falagas reviewed its use in the treatment of mycobacterial infections, including *M. tuberculosis*, and concluded that it may be beneficial in combination treatment in some cases but that its long-term use in such cases is limited by the development of serious adverse reactions.¹²⁶

Safety and tolerability

The majority of adverse events develop after prolonged administration (ie, >2 weeks) and subside shortly after discontinuation of linezolid. Adverse events associated with linezolid treatment are summarized in table 2.

Minor side effects were seen more commonly than with comparators in Phase III clinical trials: linezolid has been investigated in several comparator-controlled trials, including against ceftriaxone,¹⁰⁰ vancomycin,^{127,128} and oxacillin⁹⁷ and had a significantly higher incidence of non-serious side effects including nausea, headache, and vomiting.¹²⁹ The most common adverse event recorded in those taking linezolid was diarrhea, which occurred in 4.3% patients on linezolid, however, this was not significantly greater than in patients on the comparator drugs.¹²⁹ A Phase III randomized, comparator-controlled study in children aged 0–12 years

receiving vancomycin or linezolid for a variety of infections showed linezolid to be better tolerated than vancomycin, with significantly more drug-related adverse events in those taking vancomycin; the most commonly reported adverse events for linezolid were fever (14%), diarrhea (11%), and vomiting (9%).¹³⁰ Other adverse events potentially related to linezolid therapy include fungal infections (moniliasis), tongue discoloration and taste alterations, dizziness, insomnia, rash, and *C. difficile*-related diarrhea.¹³¹

Allergic reactions

Immediate hypersensitivity reactions to linezolid have been rarely reported.¹³² Delayed hypersensitivity reactions are also rare, including angioedema and rash.^{133,134} Cases of interstitial nephritis and DRESS syndrome have been reported.^{135,136}

Lactic acidosis

Linezolid has been reported to be associated with lactic acidosis in both adults¹³⁷ and children.¹³⁸ It is most commonly reported after prolonged administration of linezolid and resolves when linezolid is stopped^{133,137} but there have been case reports of lactic acidosis occurring early on during linezolid treatment.^{139,140} Linezolid is proposed to cause hyperlactatemia by inhibiting mitochondrial protein synthesis:¹⁴¹ it has been shown that oxazolidinones are able to bind to human mitochondrial ribosomes²⁴ and that prolonged linezolid treatment can reversibly inhibit mitochondrial protein synthesis.¹⁴² It is possible that some patients are more susceptible to developing linezolid-induced lactic acidosis due to mitochondrial DNA polymorphisms.¹⁴³

Hematological

Preclinical animal studies and Phase I healthy volunteer trials showed a moderate, reversible, dose-dependent decrease in red cell and platelet indices.¹⁴⁴ There have been several case reports of myelosuppression, including thrombocytopenia and anemia, with linezolid treatment, and one case report of reversible pure red cell aplasia after 8 weeks of linezolid treatment.¹⁴⁵ Atassi et al observed a decrease in platelets by at least 30% from baseline in 47% (9/19) patients in a single center retrospective case series.¹⁴⁶ However, results from comparator clinical trials are conflicting, with some demonstrating a myelosuppressive effect of linezolid compared to comparator drug, and others showing no difference in myelosuppression in patients on linezolid from those on comparator drug. Gerson et al looked at the hematological indices in patients on linezolid and on comparator drugs in seven clinical trials, with over 2000 patients in each arm, and

Table 2 Summary of adverse events associated with linezolid treatment

Description	Comments
Minor reactions	
Include diarrhea, nausea, headache, taste disturbances, dizziness	Minor side-effects seen more commonly in phase III trials than with comparator drugs. ¹²⁹
Allergic reactions	
Immediate hypersensitivity	Reaction after 1st dose of linezolid. ¹³²
Delayed hypersensitivity	Purpuric rash reported on day of 9 linezolid. ¹³³
Interstitial nephritis	Esposito et al. ¹³⁵
DRESS syndrome	Developed after day 7 of linezolid. ¹³⁶
Lactic acidosis	
Increased blood lactate levels (>4–5 mmol/L) with metabolic acidosis	Usually associated with prolonged linezolid treatment and resolves when linezolid is stopped. Linezolid thought to cause lactic acidosis via inhibition of mitochondrial protein synthesis. Some patients more susceptible due to polymorphisms in mitochondrial DNA.
Hematological	
Myelosuppression	Effects are mainly on red cell and platelet lineages, usually moderate, reversible and dose-dependent in case reports and phase I trials. ¹⁴⁴ Conflicting results from CCTs and meta-analyses; some suggest increased incidence of hematological side-effects compared to comparator drugs, ¹⁴⁹ others suggesting no significant difference. ¹⁴⁷
Thrombocytopenia	Commonest reported hematological side-effect. ⁹² Some reports suggest related to length of treatment. ¹⁴⁶ Reports of more severe thrombocytopenia developing in patients with impaired renal function ¹⁵⁴ possibly due to impaired renal clearance ¹⁵⁵ and higher linezolid AUC. ¹⁵⁶ Has been used in HSCT patients without delaying platelet engraftment (Cohen et al ¹⁵⁷).
Anemia	Marrow appearances suggest anemia occurs due to bone marrow suppression (Bernstein et al ¹⁵⁰). A transient delay in neutrophil recovery was reported in oncology patients with baseline marrow suppression (Jaksic et al ¹²³) but it was not reflected in length of antibiotic treatment required. Has been used in HSCT patients without delaying neutrophil engraftment. ¹⁵⁷
Pure red cell aplasia	1 case report after 8 weeks linezolid. ¹⁴⁵
Hepatic dysfunction	
Raised transaminases	Meta-analysis of 7 comparator controlled trials found mean transaminase levels stayed within normal range during treatment, and no significant difference in transaminases in patients receiving comparator drug. ¹²⁹
Microvesicular steatosis	Case report in a patient on prolonged linezolid treatment. ¹⁵⁸
Neurological toxicity	
Peripheral neuropathy	Usually presents as parasthesia with sensory loss, often painful. May be irreversible or take months to recover. ^{160,161}
Optic neuropathy	Presents with acute LOV, loss of colour vision and visual acuity. Recovery occurs more often than peripheral neuropathy does. ¹⁶² Both types may co-exist and usually occur after prolonged treatment. ¹⁵⁹
Bell's Palsy	Case report. ¹⁶⁵
Cardiac	
QTc interval	No effect in phase I studies. ¹²⁹
Pregnancy	No controlled studies performed.
Drug interactions	
Serotonin syndrome	Potential interaction with serotonergic and adrenergic drugs because linezolid is a mild MAOI. Several case reports of SS when co-administered with SSRIs. A retrospective review of patients concluded linezolid and SSRIs may be taken concomitantly if monitored for development of SS. ¹⁷¹ Review of data from phase III and IV CCTs found no increased risk of SS in patients on linezolid or comparator. ¹⁷⁰
Cytochrome p450 interactions	Linezolid is not an inhibitor or substrate of p450. ¹⁶⁵

Abbreviations: DRESS, drug rash with eosinophilia and systemic symptoms; LOV, loss of vision; MAOI, monoamine oxidase inhibitor; CCTs, comparator controlled trials; SS, serotonin syndrome; SSRI, selective serotonin re-uptake inhibitors; AUC, area under the time-concentration curve; HSCT, hemopoietic stem cell transplant.

found no statistical difference in the occurrence of anemia or thrombocytopenia between the two patient sets.¹⁴⁷ When thrombocytopenia was observed in linezolid-treated patients, it was usually in those who had received more than 2 weeks' treatment. There was a statistically significant decrease in

reticulocyte indices in the linezolid group at the end of treatment but not at follow-up. Falagas et al carried out a meta-analysis of adverse events reported in >4000 patients in eight RCTs comparing linezolid to glycopeptides or beta-lactam treatment for a mean duration of 9–12 days and

found significantly more thrombocytopenia in the linezolid arm (OR: 11.72; 95% CI: 3.66–37.57), although there was not a standard definition of thrombocytopenia in the RCTs included.⁹² There was no significant difference in anemia between the two patient groups. Nasraway et al assessed the risk of thrombocytopenia in 686 patients with nosocomial pneumonia who received linezolid or vancomycin for at least 5 days in two randomized, double-blind studies and found no statistically significant differences between groups in new-onset thrombocytopenia (platelet count of $<150 \times 10^9$ platelets/L), severe thrombocytopenia (platelet count of $<50 \times 10^9$ platelets/L), or fall in platelet counts to less than the baseline.¹⁴⁸ Weigelt et al found the incidence of reported thrombocytopenia (level not defined) was statistically more common in 592 patients receiving linezolid (mean 11.8 days) then 588 patients receiving vancomycin (mean 10.9 days) for cSSTIs in a randomized, open-label, multicenter study,¹⁴⁹ occurring in 3.5% patients in the linezolid group.

Thrombocytopenia is the most commonly reported hematological adverse event and it has been proposed that it occurs due to an immune-mediated mechanism, based on bone marrow appearances, whereas anemia appears to be caused by suppression of normal erythropoiesis.¹⁵⁰ Some authors have reported a relationship between onset of thrombocytopenia and length of linezolid treatment^{146,147} although others have not observed this.¹⁵¹ In a compassionate-use program, the incidence of adverse hematologic events was higher in patients who received >14 days of linezolid therapy.¹⁵² Kuter and Tillotson reported a median time to onset of thrombocytopenia of 17 days in spontaneous reports from postmarketing surveillance in the first 6 months of linezolid use.¹⁵³

Linezolid appears to have a greater myelosuppressive effect in some patient groups; Lin et al found severe thrombocytopenia ($<100 \times 10^9$ /L) was significantly more likely to develop in patients on linezolid with raised baseline creatinine levels than in those with normal creatinine baseline levels.¹⁵⁴ It has been postulated that this may be related to decreased renal clearance of linezolid.¹⁵⁵ Tsuji et al found a significant correlation between AUC and thrombocytopenia and anemia in renal dysfunction patients.¹⁵⁶

Despite its hematological effects, linezolid appears not to have an increased risk of hematological adverse effects in patients with preexisting hematological abnormalities. Cohen et al looked at the effect of linezolid on the engraftment of platelets and neutrophils in patients undergoing hemopoietic stem cell transplants (HSCT) in a retrospective, case-controlled study: linezolid was given for at least 7 days and was started before day +8 post-transplantation. The median duration of

treatment was 14 days in the 33 linezolid-treated patients vs 16 days in the 33 vancomycin-treated patients with no significant differences between the two groups in times to neutrophil or platelet engraftment.¹⁵⁷ Jaksic et al looked at the efficacy and safety of treatment with linezolid compared to vancomycin for febrile neutropenia in a randomized, double-blind study of patients with cancer.¹²³ They found there were fewer reported overall, including hematological, drug-related adverse events (17% of 303 linezolid patients vs 24% of 300 vancomycin patients; $P=0.04$). Patients received 10–28 days of the study antibiotic. Most of the patients had hematological malignancies with absolute neutrophil count (ANC) <100 cells/mm³. Approximately 40% patients in each group received a colony-stimulating factor during the study period. There was no difference in hematological adverse events between the groups in the intention to treat (ITT) populations. They did observe a transient delay in time to ANC recovery in the linezolid group compared to the vancomycin group, which was not reflected in the duration of antibiotic treatment. There was no difference in time to platelet recovery between the two groups ($P=0.8$).

Hepatic dysfunction

Minor, reversible increases in alanine transaminase (ALT) and aspartate transaminase (AST) have been observed on linezolid treatment. A meta-analysis looking at safety data from seven controlled clinical trials comparing linezolid and comparator drugs for a variety of infections found the mean values of liver transaminases remained within the normal range throughout the course of the studies, with no statistically significant difference between linezolid and comparator drug groups.¹²⁹ De Bus et al reported a case of severe liver toxicity with microvesicular steatosis in a patient on prolonged linezolid treatment.¹⁵⁸

Neurological toxicity

Peripheral and optic neuropathy have been reported following linezolid treatment; prolonged use, usually for more than 1 month, seems to be an important risk factor.¹⁵⁹ Both neuropathies may occur in the same patient. The peripheral neuropathy is often painful, requiring treatment with amitriptyline or gabapentin, and usually presents as parasthesia with sensory loss. Peripheral neuropathy may be irreversible or may resolve after linezolid is discontinued, sometimes taking several months for recovery.^{160,161} Optic neuropathy presents with acute loss of central vision, loss of colour vision, and visual acuity and seems more likely to recover after cessation of linezolid than peripheral neuropathy.¹⁶² Treatment with corticosteroids has produced no effect or worsening of

symptoms in some cases.¹⁶² It has also been reported after short-term (16 days) linezolid use.¹⁶³ A case of Bell's palsy in a patient on linezolid has been reported.¹⁶⁴

Cardiac

Phase I studies in human volunteers have shown no effect of linezolid on QTc interval.¹²⁹

Pregnancy

There have been no controlled studies in pregnant women.

Drug interactions

Cytochrome p450 drug interactions

Linezolid is not a cytochrome p450 inhibitor or substrate.¹⁶⁵

Serotonin syndrome

Linezolid is a mild, reversible, inhibitor of monoamine oxidase and can potentially interact with serotonergic and adrenergic agents to cause serotonin syndrome (SS) and hypertension.¹⁶⁶ There have been several case reports of SS in patients receiving linezolid with concomitant selective serotonin re-uptake inhibitors (SSRI)^{167,168} although no cases were reported in pre-marketing trials when linezolid was co-administered with several potentially interacting drugs.¹⁶⁹ Some authors have proposed that linezolid should not be used in patients who have been receiving SSRIs until the SSRI has been discontinued for 2 weeks,¹⁶⁷ however, a review of data from Phase III and IV CCTs showed the risk of SS in patients on linezolid was no different from the risk in patients on comparator drugs.¹⁷⁰ A retrospective review of patients receiving linezolid and concomitant SSRIs concluded that linezolid may be used concomitantly with SSRIs, with careful monitoring for signs and symptoms of serotonin syndrome and stopping the SSRI if SS was suspected.¹⁷¹

Cost effectiveness

Several analyses have looked at the cost effectiveness of treatment with linezolid compared to other drug for different indications.

Bounthavong et al carried out a cost effectiveness analysis of linezolid, daptomycin, and vancomycin in MRSA cSSTIs using a decision analytical model based on efficacy and safety parameters.¹⁷² The total direct costs of linezolid, daptomycin, and vancomycin were USD \$18,057, \$20,698, and \$23,671, respectively. The cost-effectiveness ratios for linezolid, daptomycin, and vancomycin were calculated to be \$37,604, \$44,086, and \$52,663 per successfully treated

patient, respectively. They concluded that linezolid appears to be more cost effective compared to daptomycin and vancomycin for MRSA cSSTIs. Schürmann et al also evaluated the cost effectiveness of linezolid against vancomycin in the empirical treatment of cSSTI due to suspected MRSA.¹⁷³ They concluded that the average total cost/episode was €8,232 for linezolid versus €9,206 for vancomycin; the higher acquisition cost of linezolid being offset by shorter inpatient stays and shorter lengths of iv treatment duration with linezolid compared to vancomycin.

De Cock et al compared the cost effectiveness of linezolid to vancomycin in suspected MRSA nosocomial pneumonia.¹⁷⁴ They found that the average total costs per episode for linezolid- and vancomycin-treated patients were €12,829 and €12,409, respectively, with a similar mean length of stay for both drugs (11.2 vs 10.8 days). They concluded that the use of linezolid was associated with a higher cure rate (73.6% vs 64.9%, respectively) and lower death rate (20.7% vs 33.9%), at an additional cost of €420 per treatment episode compared to vancomycin. Patanwala et al carried out a retrospective evaluation of the cost effectiveness of linezolid compared to vancomycin for treating surgical site infections (SSIs) due to MRSA.¹⁷⁵ Three treatment models were evaluated: treatment with intravenous vancomycin during hospitalization and after discharge with homecare follow-up; treatment with iv vancomycin during hospitalization, followed by oral linezolid after discharge; or treatment with oral linezolid during hospitalization and after discharge. They found that treatment with oral linezolid during hospitalization and after discharge was associated with lower costs (\$8923, \$11,479, and \$12,481, respectively) and greater effectiveness (0.867, 0.787, and 0.707, respectively) compared to the iv vancomycin/oral linezolid switch or iv vancomycin during hospitalization and at home. The costs per MRSA SSI cure were \$10,292, \$14,486, and \$17,653, respectively. They concluded that treatment with oral linezolid during hospitalization and after discharge is expected to be the most cost effective approach for treating SSIs caused by MRSA compared to treatment regimes including iv vancomycin.

Conclusion

Linezolid has been shown to be active against multiresistant pathogens and to have good efficacy in the treatment of serious Gram-positive infections. Its high oral bioavailability and equivalent intravenous-to-oral formulations lead to ease of dosing and administration, and combined with its good clinical outcomes, make it a cost effective option, allowing early discharge from hospital. There are currently only low resistance rates to

linezolid, and no cross-resistance with other antimicrobials, associated with its unique mechanism of action, making it a valuable treatment option for multidrug resistant organisms.

The potential problems of treatment with linezolid include its bacteriostatic rather than bacteriocidal action and the relatively high incidence of adverse effects, particularly with long-term use. Long-term use may also be complicated by development of resistance. However, despite its bacteriostatic action, it has been shown to be clinically useful in serious infections where traditionally bacteriocidal agents are required. Several of its adverse effects that occur with prolonged use are reversible and in some clinical situations, the benefits of linezolid treatment may outweigh the potential risks.

Newer oxazolidinones are currently being developed that may have better safety profiles and less resistance than linezolid.

Disclosure

The authors report no conflicts of interest in this work.

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