



Department of Vermont Health Access

Therapeutic Class Review Oxazolidinones

Overview/Summary

Linezolid is the only agent in the oxazolidinone class of antibiotics, and it is not available generically. Linezolid is bacteriostatic against enterococci and staphylococci, and bactericidal against most strains of streptococci. It acts early in translation by binding to a site on the bacterial 23S ribosomal ribonucleic acid of the 50S subunit and preventing the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process.¹ Linezolid is available both orally (tablet and powder for suspension) and intravenously. It is indicated for uncomplicated and complicated skin and skin structure infections and community- and hospital-acquired pneumonia, as well as vancomycin-resistant *Enterococcus* infections.² Linezolid has demonstrated similar clinical efficacy in the treatment of its Food and Drug Administration-approved indications compared to other agents.³⁻¹¹ The bioavailability is 100% for both the oral and intravenous formulations of linezolid, and some data supports a shorter length of hospital stay for patients treated with linezolid compared to other agents only available intravenously.¹²⁻¹³ Generally, guidelines recommend reserving linezolid use for infections caused by methicillin-resistant *Staphylococcus aureus*.¹⁴⁻²⁰

This review will focus on the oral oxazolidinones. Linezolid is only available as the branded agent Zyvox[®].

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Linezolid (Zyvox [®])	Oxazolidinones	-

Linezolid has been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration-approved indications for linezolid that are noted in Table 3. Linezolid may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to Linezolid²

Bacteria	Linezolid
Gram-Positive Aerobes	
<i>Enterococcus faecium</i>	✓
<i>Staphylococcus aureus</i> (methicillin-susceptible)	✓
<i>Staphylococcus aureus</i> (methicillin-resistant)	✓
<i>Streptococcus agalactiae</i> (Group B streptococci)	✓
<i>Streptococcus pneumoniae</i>	✓*
<i>Streptococcus pyogenes</i> (Group A streptococci)	✓

*Includes multi-drug resistant *Streptococcus pneumoniae*; refers to isolates resistant to ≥ 2 of the following: penicillin, second generation cephalosporins, macrolides, tetracyclines, and sulfamethoxazole/trimethoprim.

Indications**Table 3. Food and Drug Administration Approved Indications²**

Indication	Linezolid
Community-acquired pneumonia	✓
Complicated skin and skin structure infections	✓
Nosocomial pneumonia	✓
Uncomplicated skin and skin structure infections	✓
Vancomycin-resistant <i>Enterococcus Faecium</i> infections	✓

Pharmacokinetics**Table 4. Pharmacokinetics²**

Generic Name	Bioavailability (%)	Metabolism	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Linezolid	100	Hepatic (minimal)	30	None	1.5 to 5.6

Clinical Trials

Linezolid has demonstrated efficacy compared to other agents used for the same Food and Drug Administration-approved indications.³⁻¹¹ Specifically, linezolid has similar efficacy to vancomycin for the treatment of community-acquired and nosocomial pneumonia and complicated and uncomplicated skin and skin structure infections.^{3-5,8,9} For the treatment of vancomycin-resistant *Enterococcus Faecium*, linezolid did not have a significantly different clinical response compared to quinupristin/dalfopristin.⁷

Table 5. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Pneumonia				
Kalil et al ³ Linezolid vs vancomycin or teicoplanin*	MA Patients with nosocomial pneumonia	N=2,329 ≤28 days	Primary: Clinical cure, microbiological eradication, mortality, gastrointestinal events, renal failure and thrombocytopenia Secondary: Not reported	Primary: When linezolid was compared to vancomycin or teicoplanin, there were no significant differences in clinical cure (RR, 1.01; 95% CI, 0.93 to 1.10; <i>P</i> =0.83), microbiological eradication (RR, 1.10; 95% CI, 0.98 to 1.22; <i>P</i> =0.10) and mortality (RR, 0.95; 95% CI, 0.76 to 1.18; <i>P</i> =0.63). There was also no significant difference in microbiological eradication in patients with MRSA between linezolid and vancomycin or teicoplanin (RR, 1.10; 95% CI, 0.87 to 1.38; <i>P</i> =0.44). When compared to vancomycin or teicoplanin, linezolid was associated with significantly higher gastrointestinal events (RR, 2.02; 95% CI, 1.10 to 3.70; <i>P</i> =0.02) and thrombocytopenia (RR, 1.93; 95% CI, 1.30 to 2.87; <i>P</i> =0.001). When vancomycin or teicoplanin were compared to linezolid, there was no significant increase in the risk for renal failure (RR, 0.89; 95% CI, 0.56 to 1.43; <i>P</i> =0.64). Secondary: None reported
Walkey et al ⁴ Linezolid vs Glycopeptides (vancomycin or teicoplanin*)	MA Patients diagnosed with pneumonia	N=1,641 Up to 28 days	Primary: Clinical success at test of cure in clinically evaluable patients Secondary: Clinical success at test of cure in the ITT population, clinical success at end of treatment for clinically evaluable patients, microbiologic	Primary: There was no significant difference in clinical success at test of cure with linezolid compared to glycopeptides (RR, 1.04; 95% CI, 0.97 to 1.11; <i>P</i> =0.28). Secondary: There were no significant differences between linezolid and glycopeptides in clinical success at end of treatment (RR, 1.04; 95% CI, 0.98 to 1.11; <i>P</i> value not reported) and test of cure (RR, 1.02; 95% CI, 0.93 to 1.12; <i>P</i> =0.63). There was no significant difference in clinical success at test of cure between the two groups in patients with MRSA (RR, 1.23; 95% CI, 0.93 to 1.57; <i>P</i> =0.09) and patients without MRSA (RR, 0.95; 95% CI, 0.83 to 1.09; <i>P</i> =0.48). There was also no significant difference between linezolid and glycopeptides in mortality (RR, 0.91; 95% CI, 0.69 to 1.18; <i>P</i> =0.47), microbiologic success (RR, 1.13; 95% CI, 0.97 to 1.31; <i>P</i> =0.12) and adverse events (RR, 0.96; 95% CI, 0.86

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			success, all-cause mortality in the ITT population, drug-related adverse events in the ITT population	to 1.07; $P=0.48$). Risk for thrombocytopenia (RR, 2.97; 95% CI, 0.81 to 10.94; $P=0.10$) and renal impairment (RR, 1.09; 95% CI, 0.35 to 3.38; $P=0.89$) were not significantly different between the two groups.
Skin and Skin Structure Infections				
<p>Dodds et al⁵</p> <p>Linezolid 600 mg PO or IV BID or 10 mg/kg PO or IV every 8 hours</p> <p>vs</p> <p>vancomycin 1 g IV every 12 hours or 10 to 15 mg/kg every 6 to 25 hours</p>	<p>MA</p> <p>Hospitalized patients with skin and soft tissue infections due to hospital-acquired MRSA</p>	<p>N=813</p> <p>7 to 28 days</p>	<p>Primary: Clinical cure and microbiological cure</p> <p>Secondary: Not reported</p>	<p>Primary: There was no significant difference in clinical cure between linezolid and vancomycin treated patients (RR, 0.34; 95% CI, 0.04 to 2.89; $P=0.32$); however, there was substantial heterogeneity between the studies analyzed.</p> <p>There was no significant difference in microbiological cure between linezolid and vancomycin (RR, 0.55; 95% CI, 0.30 to 1.01; $P=0.05$).</p> <p>Secondary: Not reported</p>
<p>Stevens et al¹⁰</p> <p>Oxacillin 2 g IV every 6 hours for 10 to 21 days; patients were switched to PO dicloxacillin 500 mg orally every 6 hours at the discretion of the investigators</p> <p>vs</p> <p>linezolid 600 mg IV every 12 hours for 10 to 21 days; patients were switched to PO linezolid 600 mg every 12 hours at the discretion of the investigators</p>	<p>DB, DD, MC, PRO, RCT</p> <p>Patients 18 years of age and older with suspected gram-positive complicated skin and soft tissue infection</p>	<p>N=819</p> <p>15 to 21 days following treatment (test of cure)</p>	<p>Primary: Clinical and microbiological outcome</p> <p>Secondary: Body temperature, WBC counts, clinical signs and symptoms of infection, selected organism or pathogen eradication rates</p>	<p>Primary: Clinical cure rates at the test of cure visit were comparable between the linezolid and oxacillin and dicloxacillin groups (69.8 and 64.9% respectively; $P=0.141$).</p> <p>Microbiological success rates at the test of cure visit were similar between the linezolid and oxacillin and dicloxacillin groups (88.1 and 86.1% respectively; $P=0.606$).</p> <p>Secondary: Mean changes in temperature, WBC count and absolute neutrophil count in both treatment groups were consistent with resolution of the infection.</p> <p>A comparable improvement in clinical signs and symptoms of infection was observed between groups (P value not reported).</p> <p>Eradication rates for <i>S aureus</i>, <i>S pyogenes</i>, and <i>S agalactiae</i> were comparable between groups ($P\geq 0.097$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Patients requiring empiric gram-negative coverage were treated with aztreonam 1 to 2 g IV TID or QID.</p>				
<p>Wible et al¹¹</p> <p>Cefadroxil 15 mg/kg every 12 hours or 500 mg every 12 hours (patients 12 to 17 years of age)</p> <p>vs</p> <p>linezolid 10 mg/kg every 12 hours or 600 mg every 12 hours (patients 12 to 17 years of age)</p>	<p>DB, PRO, RCT</p> <p>Patients 5 to 17 years of age with skin infections</p>	<p>N=508</p> <p>10 to 21 days after last dose of study medication</p>	<p>Primary: Clinical cure, microbiological cure</p> <p>Secondary; Not reported</p>	<p>Primary: No significant difference was observed between groups in clinical cure (90% for cefadroxil and 91% for linezolid; $P=0.737$).</p> <p>No significant difference was observed between groups for microbiological cure (90.5% for cefadroxil and 90.4% for linezolid; $P=0.993$).</p> <p><i>S aureus</i> was eradicated in 88.8% of cefadroxil and 89.6% of linezolid treated microbiologically evaluable patients (P value not reported).</p> <p>Secondary: Not reported</p>
<p>Li et al¹²</p> <p>Linezolid 600 mg IV or PO BID</p> <p>vs</p> <p>vancomycin 1 g IV BID</p>	<p>MC, OL, RCT</p> <p>Patients with complicated skin and soft tissue infections as the primary site of MRSA infection</p>	<p>N=144</p> <p>Treatment: ≤ 4 weeks</p> <p>Observation: ≤ 4 weeks</p>	<p>Primary: Length of hospital stay</p> <p>Secondary: Not reported</p>	<p>Primary: In the clinically evaluable population, the unadjusted mean length of hospital stay was 5.3 days shorter with linezolid vs vancomycin (15.7 vs 21.0 days, respectively; $P=0.0025$). After adjusting for baseline variables, the between-treatment difference in mean length of hospital stay increased to 6.5 days with linezolid vs vancomycin (14.3 vs 20.8 days, respectively; $P<0.001$).</p> <p>Mean duration of IV therapy was shorter in the linezolid group (5.8 vs 12.6 days; $P<0.0001$).</p> <p>Clinically evaluable patients had to be treated for ≥ 7 days, which may have extended the length of hospital stay for patients receiving vancomycin IV as compared to the linezolid group that had the option to switch to PO therapy.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Itani et al¹³</p> <p>Linezolid 600 mg IV or PO every 12 hours</p> <p>vs</p> <p>vancomycin 1 g IV every 12 hours</p>	<p>MC, OL, RCT</p> <p>Hospitalized patients with complicated skin and soft tissue infections due to MRSA</p>	<p>N=1,200</p> <p>7 days</p>	<p>Primary: Length of stay, duration of IV treatment, and hospital discharge rates</p> <p>Secondary: Not reported</p>	<p>Primary: Linezolid was associated with a shorter length of stay ($P<0.01$), decreased duration of IV antibiotic therapy ($P<0.0001$), and higher rates of hospital discharge ($P<0.05$) as compared to vancomycin.</p> <p>Secondary: Not reported</p>
Vancomycin-resistant <i>E faecium</i>				
<p>El-Khoury et al⁶</p> <p>Linezolid 600 mg IV or PO BID</p> <p>Patients weighing <40 kg were dosed 10 mg/kg BID.</p>	<p>MC, OL</p> <p>Compassionate-use trial</p> <p>Solid organ transplant patients with VRE</p>	<p>N=85</p> <p>Precise duration of therapy not specified</p> <p>(23.5 days for cured patients)</p>	<p>Primary: Clinical resolution of infection</p> <p>Secondary: Not reported</p>	<p>Primary: Fifty-three patients (62.4%) survived with linezolid treatment (clinical resolution), whereas death occurred in 32 patients (32.9%).</p> <p>Documented negative cultures post-therapy were obtained in 47 of the patients that survived.</p> <p>Mean duration of therapy for cured patients was 23.5 days.</p> <p>Adverse reactions included thrombocytopenia (four patients), leukocytopenia (three patients), and increase in blood pressure (one patient).</p> <p>Secondary: Not reported</p>
<p>Raad et al⁷</p> <p>Linezolid 600 mg every 12 hours</p> <p>vs</p> <p>quinupristin/dalfopristin 7.5 mg/kg every 8 hours</p>	<p>OL, PRO, RCT</p> <p>Adults >18 years of age with infections caused by VRE</p>	<p>N=40</p> <p>39 months</p>	<p>Primary: Safety profile of the two drugs at time of treatment completion and follow-up</p> <p>Secondary: Efficacy of the two drugs at time of treatment completion and</p>	<p>Primary: The rate of myalgias/arthralgias in patients receiving quinupristin/dalfopristin was 33% as compared to 0% in patients receiving linezolid ($P<0.01$). All other reports of adverse effects were found to be not significant ($P>0.05$).</p> <p>Secondary: Clinical response at the end of therapy were not significantly different between patients receiving quinupristin/dalfopristin and patients receiving linezolid ($P=0.6$). There was no statistically significant difference between the number of deaths caused by infection, relapse, or microbiological response between the two treatment arms (all $P>0.05$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				follow-up
All infections				
<p>Falagas et al⁸</p> <p>Linezolid</p> <p>vs</p> <p>glycopeptides (vancomycin and teicoplanin*) or β-lactams (amoxicillin/clavulanate, ampicillin/sulbactam, cefadroxil, ceftriaxone, oxacillin, dicloxacillin)</p>	<p>MA</p> <p>Patients with complicated skin and soft tissue infections, Gram-positive infections, uncomplicated skin and soft tissue infections, nosocomial pneumonia, community-acquired pneumonia or MRSA infections</p>	<p>N=6,093</p> <p>Up to 28 days</p>	<p>Primary: Treatment success, all-cause mortality and adverse effects</p> <p>Secondary: Treatment duration, microbiological assessment and eradication of Gram-positive cocci</p>	<p>Primary:</p> <p>For all infections, linezolid had significantly higher treatment success with the ITT patients (OR, 1.23; 95% CI, 1.06 to 1.42; <i>P</i> value not reported) and clinically assessed patients (OR, 1.41; 95% CI, 1.11 to 1.81; <i>P</i>=0.006) compared to the glycopeptides or β-lactams. When only the blinded RCTs were analyzed, there was no significant difference between the treatments in the ITT patients (OR, 1.14; 95% CI, 0.95 to 1.38; <i>P</i> value not reported) and in clinically assessed patients (OR, 1.15; 95% CI, 0.89 to 1.48; <i>P</i>=0.29). Additionally, there was no significant difference in treatment success in the clinically assessed patients when linezolid was compared to vancomycin alone (OR, 1.44; 95% CI, 0.90 to 2.30) or β-lactams (OR, 11.34; 95% CI, 0.99 to 1.81).</p> <p>For the skin and soft tissue infections in the clinically assessed patients, linezolid had significantly higher treatment success compared to glycopeptides or β-lactams (OR, 1.67; 95% CI, 1.31 to 2.12; <i>P</i><0.0001).</p> <p>For bacteremia in the clinically assessed patients, linezolid had significantly higher treatment success compared to glycopeptides or β-lactams (OR, 2.07; 95% CI, 1.13 to 3.78; <i>P</i>=0.02).</p> <p>There was no significant difference between linezolid and glycopeptides or β-lactams for the treatment of pneumonia in the clinically assessed patients (OR, 1.03; 95% CI, 0.75 to 1.42; <i>P</i>=0.84). This was similar for the subset of patients with nosocomial pneumonia (OR, 1.05; 95% CI, 0.75 to 1.46; <i>P</i> value not reported).</p> <p>There was no significant difference in mortality between linezolid and glycopeptides or β-lactams in the ITT patients (OR, 0.97; 95% CI, 0.79 to 1.19; <i>P</i> value not reported).</p> <p>There were more adverse events with linezolid compared to glycopeptides or β-lactams in the ITT patients; although, the difference was not significant (OR, 1.40; 95% CI, 0.95 to 2.06; <i>P</i>=0.09). Linezolid was associated with significantly more thrombocytopenia in the ITT patients compared to glycopeptides or β-lactams</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>(OR, 11.75; 95% CI, 3.66 to 37.57; $P<0.0001$).</p> <p>Secondary: For all Gram-positive infections in the microbiologically assessed patients, linezolid had significantly higher treatment success compared to glycopeptides or β-lactams (OR, 1.34; 95% CI, 1.05 to 1.72; $P=0.02$).</p> <p>Linezolid was associated with higher rates eradication rates for <i>S aureus</i> in the microbiologically assessed patients compared to the other antibiotics (OR, 1.81; 95% CI, 1.40 to 2.34; $P<0.00001$).</p> <p>There was no significant differences in eradication rate for MRSA between linezolid and the other antibiotics (OR, 1.69; 95% CI, 0.84 to 3.41; $P=0.014$). There was also no significant difference between linezolid and vancomycin in patients with MRSA pneumonia (OR, 1.26; 95% CI, 0.54 to 2.96; P value not reported).</p> <p>There was no significant difference in eradication of enterococci species between linezolid and the other antibiotics (OR, 0.95; 95% CI, 0.33 to 2.73; $P=0.93$).</p>
<p>Shorr et al⁹</p> <p>Vancomycin 1 g IV every 12 hours</p> <p>vs</p> <p>linezolid 600 mg IV every 12 hours</p>	<p>MA (PRO, RCT)</p> <p>Patients with <i>S aureus</i> bacteremia (pneumonia 48 hours after hospital admission, complicated skin and soft tissue infections, or MRSA infections)</p>	<p>N=144</p> <p>7 to 35 days</p>	<p>Primary: Clinical cure of primary infection at end of therapy, microbiological eradication of <i>S aureus</i> bacteremia, and overall survival</p> <p>Secondary: Not reported</p>	<p>Primary: In clinically evaluable patients, incidence of cure was 55% (28/51) in patients given linezolid and 52% (25/48) in patients given vancomycin (OR, 1.12; 95% CI, 0.51 to 2.47). In the ITT population, clinical cure occurred in 28/74 (38%) patients given linezolid and 25/70 (36%) patients given vancomycin.</p> <p>In patients with MRSA bacteremia, 56% (14/25) of linezolid-treated patients and 46% (13/28) of vancomycin treated patients had a cure (OR, 1.47; 95% CI, 0.50 to 4.34).</p> <p>Microbiological success occurred in 69% of linezolid-treated patients and 73% of vancomycin-treated patients (OR, 0.83; 95% CI, 0.37 to 1.87).</p> <p>The survival rate was similar for both treatment groups in patients with MRSA bacteremia as well as overall <i>S aureus</i> bacteremia.</p> <p>Mean duration of therapy was shorter with IV linezolid than with vancomycin (8.6</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				vs 11.7 days; $P=0.004$). Linezolid was given IV >7 days after which it could be switched to PO. Secondary: Not reported

*Agent not available in the United States.

Drug regimen abbreviations: BID=twice daily, IV=intravenous, PO=oral, QID=four times daily, TID=three times daily

Study abbreviations: DB=double blind, DD=double dummy, MA=meta-analysis, MC=multicenter, OL=open-label, PRO=prospective, RCT=randomized controlled trial

Miscellaneous abbreviations: CI=confidence interval, ITT=intention to treat, MRSA=methicillin-resistant *S aureus*, OR=odds ratio, RR=relative risk, VRE=vancomycin-resistant *E faecium*,

WBC=white blood cell count

Special Populations**Table 6. Special Populations²**

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Linezolid	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Pediatric dosing provided for children ages birth to 17 years.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown

Adverse Drug Events**Table 7. Adverse Drug Events (%)²**

Adverse Event	Linezolid
Cardiovascular	
Edema	2.3
Hypertension	✓
Central Nervous System	
Convulsions	2.8
Dizziness/vertigo	0.4 to 2.0
Fever	0.5 to 14.1
Headache	0.5 to 11.3
Insomnia	2.5
Optic neuropathy	✓
Peripheral neuropathy	✓
Serotonin syndrome	✓
Dermatological	
Pruritus	0.4
Rash	0.4 to 7.0
Gastrointestinal	
Abdominal pain	0.5 to 2.4
Constipation	2.2
Diarrhea	3.8 to 11.0
Dyspepsia	✓
Gastrointestinal bleeding	2.3
Nausea	1.4 to 9.6
Vomiting	0.9 to 9.4
Hematologic	
Anemia	1.4 to 5.6
Eosinophilia	0.4 to 1.4
Leukopenia	✓
Pancytopenia	✓
Thrombocytopenia	0.3 to 12.9
Thrombocythemia	2.8
Laboratory Test Abnormalities	
Abnormal liver function tests (elevated)	0.4 to 1.3
Respiratory	
Apnea	2.3

Adverse Event	Linezolid
Cough	0.5 to 2.4
Dyspnea	3.3
Pharyngitis	0.5 to 2.9
Pneumonia	2.8
Upper Respiratory Infection	3.7 to 4.2
Other	
Fungal infection	0.1 to 1.5
Lactic acidosis	✓
Oral moniliasis	0.4 to 1.1
Peripheral neuropathy	✓
Sepsis	8
Taste alteration	0.9 to 1.8
Tongue discoloration	0.2 to 1.1
Vaginal moniliasis	1.0 to 1.6

Contraindications/Precautions

Linezolid is contraindicated in patients that have hypersensitivity to linezolid or any of its components. Linezolid should not be used in patients taking monoamine oxidase inhibitors (MAOIs) or two weeks after discontinuation of MAOIs. Unless blood pressure is closely monitored, linezolid should not be used in patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or taking directly or indirectly acting sympathomimetic agents, vasopressive agents or dopaminergic agents. Linezolid should also not be administered to patients with carcinoid syndrome and/or patients taking serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT₁ receptor agonists, meperidine or buspirone unless they are carefully monitored for serotonin syndrome.²

Patients receiving linezolid have also been noted to develop myelosuppression, and subsequent withdrawal has resulted in hematologic parameters returning to pretreatment values. For this reason, complete blood counts should be monitored weekly in all patients receiving linezolid therapy, and especially in those with pre-existing risk factors and those receiving prolonged treatment for >14 days.²

Linezolid should not be used for the treatment of patients with catheter-related blood stream infections or catheter-site infections. In addition, linezolid has no activity against Gram-negative pathogens and appropriate therapy should be administered if concomitant Gram-negative pathogen is found. Lactic acidosis, peripheral and optic neuropathy and convulsions have been reported in patients taking linezolid.²

Drug Interactions

Table 8. Drug Interactions^{2,21}

Generic Name	Interacting Medication or Disease	Potential Result
Linezolid	Indirect-acting sympathomimetics agents, vasopressor or dopaminergic agents	Concomitant administration may lead to hypertensive crisis.
Linezolid	Monoamine oxidase inhibitors, selective serotonin re-uptake inhibitors, buspirone, 5-HT ₁ agonists	Concomitant administration may lead to central nervous system toxicity or serotonin syndrome.

Dosage and Administration

Table 9. Dosing and Administration²

Generic Name	Adult Dose	Pediatric Dose	Availability
Linezolid	<u>Community-acquired pneumonia, complicated skin and skin structure</u>	<u>Community-acquired pneumonia, complicated skin and skin structure infection, nosocomial pneumonia;</u>	Powder for oral suspension:

Generic Name	Adult Dose	Pediatric Dose	Availability
	<p><u>infection, nosocomial pneumonia:</u> Powder for oral suspension/tablet: 600 mg every 12 hours for 10 to 14 days</p> <p><u>Uncomplicated skin and skin structure infection:</u> Powder for oral suspension/tablet: 400 mg every 12 hours for 10 to 14 days</p> <p><u>Vancomycin-resistant <i>Enterococcus faecium</i> infection:</u> Powder for oral suspension/tablet: 600 mg every 12 hours for 14 to 28 days</p>	<p>Powder for oral suspension/tablet: birth to 11 years of age, 10 mg/kg every 8 hours for 10 to 14 days; >12 years of age, 600 mg every 12 hours for 10 to 14 days</p> <p><u>Uncomplicated skin and skin structure infection:</u> Powder for oral suspension/tablet: Birth to four years of age, 10 mg/kg every 8 hours for 10 to 14 days; five to 11 years of age, 10 mg/kg every 12 hours for 10 to 14 days; >12 years of age, 600 mg every 12 hours for 10 to 14 days</p> <p><u>Vancomycin-resistant <i>Enterococcus Faecium</i> infection:</u> Powder for oral suspension/tablet: Birth to 11 years of age, 10 mg/kg every 8 hours for 14 to 28 days; >12 years of age, 600 mg every 12 hours for 14 to 28 days</p>	<p>100 mg/5 mL</p> <p>Oral tablet: 600 mg</p>

Clinical Guidelines

The clinical guidelines contained in Table 10 are summarized globally and are not limited to the role of the oxazolidinones.

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
<p>Infectious Diseases Society of America/ American Thoracic Society: Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)¹⁴</p>	<p><u>General recommendations</u></p> <ul style="list-style-type: none"> • Selection of antimicrobial regimens for empirical therapy is based on prediction of the most likely pathogens(s) and knowledge of local susceptibility patterns. • Once the etiology of community acquired pneumonia has been identified via microbiological testing, antimicrobial therapy should be directed at that pathogen. <p><u>Empiric therapy - outpatient treatment</u></p> <ul style="list-style-type: none"> • For previously healthy patients with no risk factors for drug resistant <i>Streptococcus pneumoniae</i> infection, a macrolide (azithromycin, clarithromycin, or erythromycin) can be used. Doxycycline may also be an alternate option. • A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) is the treatment option in regions with a high rate of macrolide-resistant <i>S pneumoniae</i>, or for patients with comorbidities, such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressive conditions or use of immunosuppressive drugs. Fluoroquinolones may also be used for patients who have used antimicrobials within the previous three months. Other preferred options for these patients would be the combination of a β-lactam (ceftriaxone, cefpodoxime, or cefuroxime) plus a macrolide or doxycycline, or amoxicillin/clavulanate.

Clinical Guideline	Recommendations
	<p><u>Empiric therapy - inpatient, non-intensive care unit treatment</u></p> <ul style="list-style-type: none"> • A respiratory fluoroquinolone or a combination of a β-lactam plus a macrolide is recommended. • Preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem may also be used for selected patients. • A respiratory fluoroquinolone should be used for penicillin allergic patients. <p><u>Empiric therapy - inpatient, intensive care unit treatment</u></p> <ul style="list-style-type: none"> • A β-lactam (cefotaxime, ceftriaxone, or ampicillin/sulbactam) plus either azithromycin or a respiratory fluoroquinolone. • For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended. • For <i>Pseudomonas</i> infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin/tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin. • The antipneumococcal, antipseudomonal β-lactams listed above can also be used with either an aminoglycoside and azithromycin, or an aminoglycoside and an antipneumococcal fluoroquinolone. • For penicillin-allergic patients, substitute aztreonam for the above β-lactam for <i>Pseudomonas</i> infection. <p><u>Pathogen-directed therapy</u></p> <ul style="list-style-type: none"> • <i>S pneumonia</i> (penicillin non-resistant)- penicillin G or amoxicillin preferred; alternative agents include macrolides, cephalosporins (oral cefpodoxime, cefprozil, cefuroxime, cefdinir, cefditoren or parenteral cefuroxime, ceftriaxone or cefotaxime), clindamycin, doxycycline or a respiratory fluoroquinolone. • <i>S pneumonia</i> (penicillin resistant)- agents chosen based on susceptibility; alternative agents include vancomycin, linezolid and high-dose amoxicillin (3 g/day). • <i>Haemophilus influenza</i> (non-β-lactamase producing)- amoxicillin preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin. • <i>H influenza</i> (β-lactamase producing)- second- or third-generation cephalosporin or amoxicillin/clavulanate preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin. • <i>Mycoplasma pneumonia/Chlamydia pneumonia</i>- macrolide, tetracycline preferred; alternative agent is fluoroquinolone. • <i>Legionella</i> species- fluoroquinolone, azithromycin preferred; alternative agent is doxycycline. • <i>Chlamydia psittaci</i>- tetracycline preferred; alternative agent is a macrolide. • <i>Coxiella burnetii</i>- tetracycline preferred; alternative agent is a macrolide. • <i>Francisella tularensis</i>- doxycycline preferred; alternative agents include gentamicin or streptomycin. • <i>Yersinia pestis</i>- streptomycin, gentamicin recommend; alternative agents include doxycycline or fluoroquinolone. • <i>Bacillus anthracis</i> (inhalation)- ciprofloxacin, levofloxacin, doxycycline preferred (usually with a second agent); alternative agents include other fluoroquinolones, rifampin, clindamycin, chloramphenicol, or a β-lactam if susceptible. • <i>Enterobacteriaceae</i>- third generation cephalosporin, carbapenem; alternative agents include a β-lactam/β-lactamase inhibitor or a fluoroquinolone.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • <i>Pseudomonas aeruginosa</i>- antipseudomonal β-lactam plus ciprofloxacin or levofloxacin or aminoglycoside preferred; alternative agents include aminoglycoside plus ciprofloxacin or levofloxacin. • <i>Burkholderia pseudomallei</i>- carbapenem, ceftazidime preferred; alternative agents include fluoroquinolone or sulfamethoxazole/trimethoprim (SMX/TMP). • <i>Acinetobacter</i> species- carbapenem preferred; alternative agents include cephalosporin and aminoglycoside, ampicillin/sulbactam, colistin. • <i>Staphylococcus aureus</i> (methicillin susceptible)- antistaphylococcal penicillin preferred; alternative agents include cefazolin and clindamycin. • <i>S aureus</i> (methicillin resistant)- vancomycin or linezolid preferred; alternative agent is SMX/TMP. • <i>Bordetella pertussis</i>- macrolide preferred; alternative agent is SMX/TMP. • Anaerobe (aspiration)- β-lactam/β-lactamase inhibitor or clindamycin preferred; alternative agent is carbapenem. • Influenza virus- oseltamivir or zanamivir preferred. • <i>Mycobacterium tuberculosis</i>- isoniazid plus rifampin plus ethambutol plus pyrazinamide preferred. • <i>Coccidioides</i> species- no therapy generally recommended in normal host for uncomplicated infection; if therapy desired, itraconazole or fluconazole preferred; alternative agent is amphotericin B. • <i>Histoplasmosis</i>- itraconazole preferred; alternative agent is amphotericin B. • <i>Blastomycosis</i>- itraconazole preferred; alternative agent is amphotericin B. • Suspected H1N1 pandemic influenza should be treated with oseltamivir and antibacterial agents targeting <i>S pneumonia</i> and <i>S aureus</i>.
<p>American College of Chest Physicians: Management of Community-Acquired Pneumonia in the Home: An American College of Chest Physicians Clinical Position Statement (2005)¹⁵</p>	<ul style="list-style-type: none"> • The oral route for medications is recommended if the patient can tolerate it, and if the availability and activity of the agents are adequate. • Severity of illness, patient age, comorbidities, concomitant medications, and ease of administration are all factors that can impact the empiric treatment decision. • The use of a macrolide, doxycycline, or fluoroquinolone antibacterial agent is recommended by both the Infectious Disease Society of America and the American Thoracic Society consensus guidelines as appropriate empiric outpatient treatment for low-risk patients. • Amoxicillin/clavulanate and some second generation cephalosporins (cefuroxime, cefpodoxime, or cefprozil) are alternatives for low-risk patients. • A patient who is at high risk either because of complicated comorbidities or extensive prior antibiotic use may be a candidate for treatment with a β-lactam/macrolide combination or an antipseudomococcal fluoroquinolone. • Double therapy with either a β-lactam/macrolide combination or a β-lactam/antipseudomococcal fluoroquinolone should be considered in patients who would normally be considered for intensive care unit admission but have chosen to remain in the home.
<p>Infectious Diseases Society of America/ American Thoracic Society: Guidelines for the Management of Adults with Hospital-acquired,</p>	<ul style="list-style-type: none"> • Empiric therapy for hospital-acquired pneumonia, ventilator-associated pneumonia and healthcare-associated pneumonia should include agents from a different class than the patient has recently received. • Judicious use of combination therapy in hospital-acquired pneumonia for a specific pathogen is recommended with consideration of short-duration (five days) aminoglycoside therapy when used in combination with β-lactam to treat <i>P aeruginosa</i> pneumonia. • De-escalation of antibiotics should be considered once results are

Clinical Guideline	Recommendations
Ventilator-associated, and Healthcare-associated Pneumonia (2004) ¹⁶	<p>available of lower respiratory tract cultures and patient's clinical response.</p> <ul style="list-style-type: none"> For patients with uncomplicated hospital-acquired pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia who have received initially appropriate therapy and have had a good clinical response with no evidence of infection with nonfermenting gram-negative bacilli, a shorter duration of antibiotic therapy (seven to eight days) is recommended. The following initial empiric therapy is recommended for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with early onset of disease, no known risk factors for multidrug-resistant pathogens and any disease severity: ceftriaxone, levofloxacin, moxifloxacin, ciprofloxacin, ampicillin/sulbactam or ertapenem. The following initial empiric therapy is recommended for hospital-acquired pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia in patients with late onset of disease or known risk factors for multidrug-resistant pathogens and all disease severity: antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam/ β-lactamase inhibitor (piperacillin/tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin or tobramycin) plus linezolid or vancomycin.
Infectious Diseases Society of America: Practice Guidelines for the Management of Bacterial Meningitis (2004) ¹⁷	<p><u>Antimicrobial therapy based on the presumptive pathogen identified by positive Gram stain</u></p> <ul style="list-style-type: none"> <i>S pneumoniae</i> - vancomycin plus third-generation cephalosporin; alternative agents are meropenem or a fluoroquinolone. <i>Neisseria meningitidis</i> - third generation cephalosporin; alternative agents include penicillin G, ampicillin, chloramphenicol, fluoroquinolones, or aztreonam. <i>Listeria monocytogenes</i> and <i>Streptococcus agalactiae</i> - ampicillin or penicillin G; alternative agents include SMX/TMP or meropenem (for <i>L monocytogenes</i>) and a third generation cephalosporin (for <i>S agalactiae</i>). <i>H influenzae</i> - third generation cephalosporin; alternative agents include chloramphenicol, cefepime, meropenem, or a fluoroquinolone. <i>Escherichia coli</i> - third generation cephalosporin; alternative agents include cefepime, meropenem, aztreonam, fluoroquinolone, or SMX/TMP. <p><u>Empiric therapy based on age and predisposing condition</u></p> <ul style="list-style-type: none"> Age <one month, <i>S agalactiae</i>, <i>E coli</i>, <i>L monocytogenes</i>, <i>Klebsiella</i> species: ampicillin plus cefotaxime or ampicillin plus aminoglycoside. Age one to 23 months, <i>S pneumoniae</i>, <i>N meningitidis</i>, <i>S agalactiae</i>, <i>H influenzae</i>, <i>E coli</i>: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime). Age two to 50 years, <i>N meningitidis</i>, <i>S pneumoniae</i>: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime). Age >50 years, <i>S pneumoniae</i>, <i>N meningitidis</i>, <i>L monocytogenes</i>, aerobic gram-negative bacilli: vancomycin plus ampicillin plus third generation cephalosporin (ceftriaxone or cefotaxime). Basilar skull fracture, <i>S pneumoniae</i>, <i>H influenzae</i>, group A β-hemolytic streptococci: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime). Penetrating head trauma, <i>S aureus</i>, coagulase-negative staphylococci, aerobic gram-negative bacilli: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus meropenem.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Post-neurosurgery, aerobic gram-negative bacilli, <i>S aureus</i>, coagulase-negative staphylococci: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus meropenem. • Cerebrospinal fluid shunt, coagulase-negative staphylococci, <i>S aureus</i>, aerobic gram-negative bacilli, <i>Propionibacterium acnes</i>: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus meropenem. <p><u>Specific antimicrobial therapy based on pathogen and susceptibility</u></p> <ul style="list-style-type: none"> • <i>S pneumoniae</i>: <ul style="list-style-type: none"> ○ Penicillin minimum inhibitory concentration (MIC) <0.1 µg/mL: penicillin G or ampicillin, alternative therapies include third generation cephalosporin (ceftriaxone or cefotaxime), chloramphenicol. ○ Penicillin MIC 0.1 to 1.0 µg/mL: third generation cephalosporin (ceftriaxone or cefotaxime), alternative agents include cefepime, meropenem. ○ Penicillin MIC ≥2 µg/mL: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime, consider addition of rifampin if MIC of ceftriaxone is >2µg/mL), alternative agent is fluoroquinolone (gatifloxacin or moxifloxacin). ○ Cefotaxime or ceftriaxone MIC ≥1 µg/mL: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime, consider addition of rifampin if MIC of ceftriaxone is >2 µg/mL), alternative agent is fluoroquinolone (gatifloxacin or moxifloxacin). • <i>N meningitidis</i>: <ul style="list-style-type: none"> ○ Penicillin MIC <0.1 µg/mL: penicillin G or ampicillin, alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime), chloramphenicol. ○ Penicillin MIC 0.1 to 1.0 µg/mL: third generation cephalosporin (ceftriaxone or cefotaxime), alternative agents include chloramphenicol, fluoroquinolone, meropenem. • <i>L monocytogenes</i>: ampicillin or penicillin G (addition of aminoglycoside should be considered), alternative agents include SMX/TMP, meropenem. • <i>S agalactiae</i>: ampicillin or penicillin G (addition of aminoglycoside should be considered), alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime). • <i>E coli</i> or <i>Enterobacteriaceae</i>: third generation cephalosporin, alternative agents include aztreonam, fluoroquinolone, meropenem, SMX/TMP, ampicillin. • <i>P aeruginosa</i>: cefepime or ceftazidime (addition of aminoglycoside should be considered), alternative agents include aztreonam, ciprofloxacin, meropenem (addition of aminoglycoside should be considered). • <i>H influenzae</i>: <ul style="list-style-type: none"> ○ β-lactamase negative: ampicillin, alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime), cefepime, chloramphenicol, fluoroquinolone. ○ β-lactamase positive: third generation cephalosporin, alternative agents include cefepime, chloramphenicol, fluoroquinolone. • <i>S aureus</i> <ul style="list-style-type: none"> ○ Methicillin susceptible: nafcillin or oxacillin, alternative agents include vancomycin, meropenem. ○ Methicillin resistant: vancomycin (consider addition of rifampin), alternative agents include SMX/TMP, linezolid. • <i>Staphylococcus epidermidis</i>: vancomycin (consider addition of rifampin),

Clinical Guideline	Recommendations
	<p>alternative agent is linezolid.</p> <ul style="list-style-type: none"> • <i>Enterococcus</i> species: <ul style="list-style-type: none"> ○ Ampicillin susceptible: ampicillin plus gentamicin. ○ Ampicillin resistant: vancomycin plus gentamicin. ○ Ampicillin and vancomycin resistant: linezolid.
<p>Infectious Diseases Society of America: Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2005)¹⁸</p>	<p><u>General observations</u></p> <ul style="list-style-type: none"> • Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first or second generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of methicillin-resistant <i>S aureus</i> (MRSA) strains. • In patients with severe infection or infection that has progressed while on empirical antibiotic treatment, selection of therapeutic agents should be based on results of the gram stain, culture and drug susceptibility analysis. • In the case of <i>S aureus</i>, the clinician should assume the organism is resistant due to the high prevalence of community-associated MRSA strains. Agents effective against MRSA should be used in patients who have severe infections requiring hospitalization or those who have not responded to attempts to eradicate the infection (vancomycin, linezolid, daptomycin). Step-down treatment to other agents may be possible based on susceptibility tests. • An increase in the macrolide resistance of <i>Streptococcus pyogenes</i> has been noted, while 99.5% of strains remain susceptible to clindamycin and 100% to penicillin. • Osteomyelitis typically requires treatment for four to six weeks. <p><u>Animal bites</u></p> <ul style="list-style-type: none"> • The decision to administer oral or intravenous antibiotic therapy is determined by the depth and severity of the wound and the time elapsed since the bite. • Appropriate first-line therapy includes oral amoxicillin/clavulanate, doxycycline, or penicillin VK plus dicloxacillin. Other options include fluoroquinolones, SMX/TMP, and cefuroxime. The patient may also require an additional agent that is active against anaerobes, such as metronidazole or clindamycin. • Intravenous options include ampicillin/sulbactam, piperacillin/tazobactam, second generation cephalosporins, and carbapenems. Second- and third-generation cephalosporins may be used but require the addition of an antianaerobic agent. <p><u>Animal contact</u></p> <ul style="list-style-type: none"> • Though no randomized controlled trials exist for treatment of cutaneous anthrax, most data indicate that penicillin is effective. Less evidence supports the use of tetracyclines, chloramphenicol and erythromycin. • Bioterrorism-related anthrax should be treated with a fluoroquinolone until susceptibility tests are available, as inhalation may also have occurred. • Cat scratch disease and bacillary angiomatosis may be treated with azithromycin, erythromycin or doxycycline. Other alternatives include rifampin, SMX/TMP and ciprofloxacin. • Erysipeloid cutaneous infections should be treated with penicillin or amoxicillin; cephalosporins, clindamycin and fluoroquinolones are effective alternatives. • Glanders may be treated with ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Streptomycin has been the drug of choice for bubonic plague. Tetracycline and chloramphenicol are also appropriate. Fluoroquinolones are alternative agents. • Ciprofloxacin has been suggested for both treatment and prevention of plague (bubonic and pneumonic) due to biowarfare agents. • Streptomycin is considered the drug of choice for tularemia. Acutely ill patients should receive streptomycin or gentamicin. Mild to moderate disease may be treated with oral tetracycline or doxycycline. <p><u>Cellulitis</u></p> <ul style="list-style-type: none"> • Cellulitis is commonly treatable with oral antibiotics, such as dicloxacillin, cephalexin, clindamycin or erythromycin. • For severe infection, the treatment of choice is either a penicillinase-resistant semisynthetic penicillin or a first generation cephalosporin. • In patients with severe penicillin allergy, clindamycin or vancomycin is indicated. • To reduce the risk of recurrence, it is important to keep the affected area well-hydrated and to reduce edema with elevation or compression stockings. Prophylactic treatment with monthly intramuscular benzathine penicillin, oral erythromycin, or penicillin V is also an option. <p><u>Erysipelas</u></p> <ul style="list-style-type: none"> • Oral or intravenous penicillin is the first-line treatment depending on severity. • In the presence or suspicion of staphylococcal infection, a penicillinase-resistant semisynthetic penicillin or a first generation cephalosporin is indicated. <p><u>Human bites</u></p> <ul style="list-style-type: none"> • Clenched-fist injuries typically require hospitalization and intravenous ampicillin/sulbactam, cefoxitin or one of the carbapenems. • Fluoroquinolones plus clindamycin or SMX/TMP plus metronidazole can be used in patients with severe penicillin allergy. <p><u>Impetigo</u></p> <ul style="list-style-type: none"> • Penicillinase-resistant penicillins or first generation cephalosporins are the preferred agents. • Erythromycin is indicated in the presence of pyoderma, but use is limited by erythromycin-resistant strains of <i>S aureus</i> and <i>S pyogenes</i>. • Topical therapy with mupirocin is equivalent to oral systemic antibiotics. <p><u>Necrotizing infections</u></p> <ul style="list-style-type: none"> • Antimicrobial therapy (coverage against aerobes and anaerobes) should be directed at the specific pathogen and appropriate doses should be used until operative procedures are no longer needed. • The combination of ampicillin/sulbactam, clindamycin and ciprofloxacin is first-line therapy for community-acquired mixed infection. The carbapenems, or a combination of cefotaxime plus metronidazole or clindamycin, are also appropriate. In cases of penicillin allergy, alternatives include clindamycin or metronidazole plus an aminoglycoside or fluoroquinolone. • Clindamycin and penicillin should be used in necrotizing fasciitis and/or streptococcal toxic shock syndrome caused by group A streptococci. The

Clinical Guideline	Recommendations
	<p>efficacy of intravenous gamma globulin in these cases is still under investigation.</p> <ul style="list-style-type: none"> • <i>Streptococcus</i> infection should be treated with high-dose penicillin or ampicillin plus clindamycin. • <i>S aureus</i> infection, often associated with pyomyositis, should be treated with nafcillin, oxacillin, or cefazolin. Vancomycin should be reserved for resistant strains or can be used in cases of severe penicillin allergy, as well as linezolid, quinupristin/dalfopristin or daptomycin. Clindamycin is limited by its potential of cross-resistance. • In gas gangrene, the efficacy of hyperbaric oxygen is inconclusive. Standard antibiotic treatment is penicillin plus clindamycin. <p><u>Soft-tissue infections caused by community-acquired MRSA</u></p> <ul style="list-style-type: none"> • They are often susceptible to non-β-lactam antibiotics, and standard treatment includes doxycycline, clindamycin, SMX/TMP, rifampin, or fluoroquinolones, specifically levofloxacin, gatifloxacin or moxifloxacin. <p><u>Surgical site infections</u></p> <ul style="list-style-type: none"> • Surgical site infections often resolve without the use of antibiotics. • In patients with a temperature $>38.5^{\circ}\text{C}$, pulse rate >100 beats/minute or erythema diameter >5 cm from incision with induration or necrosis, a short course of antibiotics is recommended. • For wounds of the perineum or operation on the gastrointestinal tract or female genital tract, cefotetan or ampicillin/sulbactam or a fluoroquinolone plus clindamycin is recommended. • For clean wounds on the trunk, head, neck or extremities, cefazolin, oxacillin or clindamycin are recommended. <p><u>Immunocompromised patients</u></p> <ul style="list-style-type: none"> • In neutropenic patients, empiric broad-spectrum antibacterial therapy is recommended at the first sign of infection including fever. • For gram-negative infections, monotherapy with carbapenems, cephalosporins with antipseudomonal activity, and piperacillin/tazobactam, are all appropriate. Recommended combination therapy regimens are (1) an aminoglycoside plus either an antipseudomonal penicillin or an extended-spectrum cephalosporin, or (2) an extended-spectrum penicillin plus ciprofloxacin. Adjunct treatment with granulocyte colony-stimulating factor or granulocyte-monocyte colony-stimulating factor is recommended. • For gram-positive infections, vancomycin is not recommended for empirical antibiotic therapy because of resistance; linezolid or daptomycin are appropriate alternatives to vancomycin. • For <i>Nocardia</i> infection, first-line therapy is SMX/TMP. Other sulfonamide antibiotics and imipenem are also appropriate. • Empirical antifungal therapy is a common practice in neutropenic patients with persistent fever. Amphotericin B, caspofungin and voriconazole are appropriate. • Amphotericin B and its lipid formulations have been the gold standard to treatment for yeast and fungal infections in neutropenic patients. Caspofungin and voriconazole appear to be as effective as amphotericin B and with less serious acute toxicity but are more expensive. • Treatment of non-tubercular mycobacterial infections of the skin and soft tissues requires combination therapy that should include a macrolide. • Cutaneous <i>Nocardia</i> infections should be treated with SMX/TMP, the

Clinical Guideline	Recommendations
	<p>treatment of choice. Other sulfa antibiotics and imipenem are also effective.</p> <ul style="list-style-type: none"> Initial therapy for Cryptococcal cellulitis is fluconazole, which is also used to complete therapy after patients have shown an initial response to amphotericin B and 5-flucytosine induction therapy. Amphotericin B is recommended in patients with cellular immune deficiency and disseminated histoplasmosis. Itraconazole may replace amphotericin B after one to two weeks to complete at least six to 12 months of treatment. Prevention of viral reactivation with oral acyclovir, famciclovir or valacyclovir is an important component of the treatment of cutaneous varicella zoster virus. Acyclovir is the treatment of choice for herpes simplex virus infections, though famciclovir and valacyclovir are also highly effective. Prolonged ganciclovir therapy is the treatment of choice for cutaneous cytomegalovirus.
<p>Infectious Diseases Society of America: Diagnosis and Treatment of Diabetic Foot Infections (2004)¹⁹</p>	<ul style="list-style-type: none"> Aerobic gram-positive cocci are the usual pathogens responsible for acute infections due to breaks in the skin. The most common pathogens identified are <i>S aureus</i> and the b-hemolytic streptococci. Chronic wounds involve more complex pathogens including enterococci, Enterobacteriaceae, anaerobes, <i>P aeruginosa</i> and non-fermentative gram-negative rods. Antibiotics are not recommended in uninfected wounds. Most patients with mild to moderate infections can be treated as outpatients. For severe infections, initial empiric antibiotic therapy should include coverage for gram-positive, gram-negative and anaerobic pathogens and should be administered parenterally. Mild to moderate infections can usually be treated with narrow-spectrum agents which cover gram-positive cocci. On the basis of available data, no single drug or drug combination appears to be “superior” to another. Cephalosporins have been used and include cefoxitin, ceftizoxime, ceftriaxone and cephalexin. Osteomyelitis typically requires four to six weeks of antibiotic therapy.
<p>Infectious Diseases Society of America: Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant <i>Staphylococcus Aureus</i> Infections in Adults and Children (2011)²⁰</p>	<p><u>Empiric therapy for community-associated MRSA in skin and soft-tissue infections</u></p> <ul style="list-style-type: none"> For outpatients oral antibiotic options include: clindamycin, SMX/TMP, a tetracycline (doxycycline or minocycline) and linezolid. If additional coverage for β-hemolytic streptococci and community acquired-MRSA is desired, options include: clindamycin alone, SMX/TMP or tetracycline in combination with a β-lactam (e.g., amoxicillin) or linezolid alone. For hospitalized patients with complicated skin and soft-tissue infections, therapy for MRSA in addition to broad-spectrum antibiotics should be considered depending on culture data. Options include: intravenous vancomycin, intravenous or oral linezolid, intravenous daptomycin, intravenous telavancin and intravenous or oral clindamycin. In hospitalized children with complicated skin and soft-tissue infections that are stable without ongoing bacteremia or intravascular infection, intravenous clindamycin (if resistance rate is low) with transition to oral therapy is recommended. Oral or intravenous linezolid is an alternative therapy.

Clinical Guideline	Recommendations
	<p><u>Therapy for MRSA bacteremia and infective endocarditis</u></p> <ul style="list-style-type: none"> • For adults with bacteremia and infective endocarditis with native valve, vancomycin or daptomycin is recommended. • For patients with infective endocarditis and prosthetic valve, vancomycin plus rifampin and gentamicin is recommended. • For children with bacteremia and infective endocarditis, vancomycin is recommended. Limited data shows daptomycin as a treatment option. <p><u>Therapy for MRSA pneumonia</u></p> <ul style="list-style-type: none"> • For health-care associated or community acquired pneumonia, intravenous vancomycin or oral or intravenous linezolid or oral or intravenous clindamycin, if the strain is susceptible is recommended. • For children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, intravenous clindamycin can be used if the clindamycin resistance is low with a transition to oral if the strain is susceptible. Linezolid is an alternative. <p><u>Therapy for bone and joint infections</u></p> <ul style="list-style-type: none"> • For osteomyelitis and septic arthritis, antibiotic options include intravenous vancomycin, intravenous daptomycin, intravenous or oral SMX/TMP with rifampin, intravenous or oral linezolid and intravenous or oral clindamycin. In patients with concurrent bacteremia, rifampin can be added to the previous agents after clearance of bacteremia. • For early-onset or acute hematogenous prosthetic joint infections involving a stable implant with short duration of symptoms and debridement, initiate therapy with parental therapy (see above) plus rifampin for two weeks followed by rifampin plus a fluoroquinolone, SMX/TMP, a tetracycline or clindamycin for three or six months. • For early-onset spinal implant infections or implants in an actively infected site, initial parental therapy plus rifampin followed by prolonged oral therapy is recommended. • For children with acute hematogenous MRSA osteomyelitis and septic arthritis, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, intravenous clindamycin can be used if the clindamycin resistance is low with a transition to oral if the strain is susceptible. Alternative agents include daptomycin or linezolid. <p><u>Therapy for MRSA infections of the central nervous system</u></p> <ul style="list-style-type: none"> • For meningitis, brain abscess, subdural empyema and spinal epidural abscess, intravenous vancomycin is recommended. Rifampin may be added to the regimen. Alternative agents include linezolid or SMX/TMP. • For children, intravenous vancomycin is recommended. <p><u>Therapy for persistent bacteremia and vancomycin treatment failures</u></p> <ul style="list-style-type: none"> • The following treatment regimens should be considered: high-dose daptomycin, if isolate is susceptible, in combination with another agent (e.g., gentamicin, rifampin, linezolid or a β-lactam antibiotic). • If reduced susceptibility to vancomycin and daptomycin is present, treatment options include: quinupristin/dalfopristin, SMX/TMP, linezolid, telavancin. <p><u>Therapy of MRSA infections in neonates</u></p>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> For localized neonatal pustulosis in a premature or very low-birthweight infant or more-extensive disease involving multiple sites in a full-term infant, intravenous vancomycin or clindamycin is recommended, at least initially, until bacteremia is excluded. For neonatal MRSA sepsis, intravenous vancomycin is recommended. Clindamycin and linezolid are alternatives for non-endovascular infections.

Conclusions

The only drug contained in the oxazolidinone class is linezolid. It is indicated for skin and skin structure infections, pneumonia and vancomycin-resistant *Enterococcus* infections. Linezolid is effective against methicillin-resistant *Staphylococcus aureus* (MRSA) and multi-drug resistant *Streptococcus pneumoniae*. Clinical success with linezolid has been shown to be similar to other available agents used for its Food and Drug Administration-approved indications. To minimize the emergence of resistance, guidelines generally recommend reserving linezolid for treatment infections due to MRSA. Because the oral and parental formulations have 100% bioavailability, patients can be switched to the oral formulation and treatment may be continued outside the hospital. Linezolid is not available generically.

Appendix I: Utilization Within This Drug Class for DVHA: April 1, 2011 to September 30, 2011

Medication	Unique Utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Zyvox®	22	28	100.00%	\$44,053.39	\$1,573.34
Class Total:	22	28	100.00%	\$44,053.39	\$1,573.34

Recommendations

In recognition of the established safety and efficacy of Zyvox®, consensus clinical guideline recommendations, unavailability of generics and cost considerations, no changes are recommended to the current Department of Vermont Health Access (DVHA) approval criteria (below).

- The patient has been started on intravenous or oral linezolid in the hospital and will be finishing the course of therapy in an outpatient setting
- OR
- The patient has a documented blood, tissue, sputum, or urine culture that is positive for Vancomycin-Resistant Enterococcus (VRE) species or Methicillin-Resistant Staphylococcus species
 - Quantity limit = 56 tablets/28 days or 60 ml suspension/day.

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