



treatment of MRSA infections

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Linezolid

Linezolid is the currently available oxazolidinone approved by the US Food and Drug administration.

Mechanism of Action

✓ *are inhibitors of protein synthesis*

and

✓ *are usually bacteriostatic .*

**Activity Against
Gram-Positive Organisms**

- ✓ **Staphylococcus aureus** (methicillin-susceptible and methicillin-resistant strains and vancomycin intermediate and vancomycin-resistant strains)
- ✓ **coagulase-negative staphylococci**
- ✓ **Enterococcus faecalis and Enterococcus faecium** (vancomycin-susceptible and vancomycin-resistant strains)
- ✓ **streptococci**, including penicillin-resistant **Streptococcus pneumoniae**

ORGANISM	LINEZOLID	
	MIC ₉₀ (µg/mL)	Susceptible (% of Strains)
<i>Staphylococcus aureus</i>		
Oxacillin-susceptible	1–2	100
Oxacillin-resistant	1–2	99.9
Coagulase-negative staphylococci		
Oxacillin-susceptible	0.5–2	99.4
Oxacillin-resistant	0.5–2	99.1
β-Hemolytic streptococci	1	100
<i>Streptococcus pneumoniae</i>	1	100
Viridans group and other streptococci	1	100
<i>Enterococcus faecalis</i>	2	100
<i>Enterococcus faecium</i>		
Vancomycin-susceptible	2	100
Vancomycin-resistant	2	98.5

*other gram-positive
organisms*

- *Corynebacterium spp.*
- *Listeria monocytogenes,*
- *Bacillus spp.,*
- *Micrococcus spp.,*
- *Erysipelothrix rhusiopathiae,*
- *Leuconostoc spp.*
- *Rhodococcus equi, and*
- *Pediococcus spp.*
- *Nocardia*



***Activity Against
Mycobacterium spp***

- ***Mycobacterium tuberculosis***

and

- ***a variety of nontuberculous
mycobacteria, such as Mycobacterium
avium complex and Mycobacterium
abscessus complex***

Pharmacology

for serious infections :

The approved dose of linezolid for adults and adolescents is 600 mg intravenously or orally every 12 hours.

uncomplicated skin and soft tissue infections :

a dose of 400 mg every 12 hours for adults

Absorption after ingestion is rapid, with peak serum levels occurring after 1 to 2 hours and bioavailability approaching 100%.

FDA-approved indications

- (1) Nosocomial pneumonia caused by (MRSA) or (MSSA) S. aureus or S. pneumoniae*
- (2) community-acquired pneumonia caused by S. pneumoniae including cases with concurrent bacteremia or MSSA*
- (3) complicated skin and skin structure infections including diabetic foot infections without concomitant osteomyelitis caused by S. aureus (MRSA or MSSA), Streptococcus pyogenes, or Streptococcus agalactiae*
- (4) uncomplicated skin and skin structure infections caused by MSSA or S. pyogenes; and*
- (5) vancomycin-resistant E. faecium infections including those with concurrent bacteremia.*

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Linezolid vs Vancomycin*

Analysis of Two Double-Blind Studies of Patients With Methicillin-Resistant
Staphylococcus aureus Nosocomial Pneumonia

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*nosocomial pneumonia
involving MRSA*

*A total of 1,019 patients with suspected Gram-positive nosocomial pneumonia, including 339 patients with documented *S aureus* pneumonia and 160 patients with documented MRSA pneumonia*

initial therapy with linezolid was associated with significantly better survival (80.0% vs 63.5%) and clinical cure rates (59.0% vs 35.5 %) than was vancomycin in patients with nosocomial pneumonia due to MRSA.

***nosocomial pneumonia
involving MRSA***

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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Linezolid versus vancomycin for the treatment of suspected methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a systematic review employing meta-analysis

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**Nine trials involving 2618 pneumonia patients were reviewed ;
suggest that linezolid is not superior to vancomycin with respect to both
clinical and microbiological cure rates in patients with MRSA NP.**

**nephrotoxicity was more frequent with vancomycin but no differences
between the treatments were found for all-cause mortality,
thrombocytopenia, gastrointestinal effects, and drug discontinuation due
to adverse events.**

CA-MRSA pneumonia

IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children

Clinical Infectious Diseases 2011;52(3):e18–e55

For hospitalized patients with severe community acquired pneumonia defined by any one of the following:

- (1) a requirement for (ICU) admission,***
- (2) necrotizing or cavitary infiltrates, or***
- (3) empyema, empirical therapy for MRSA is recommended pending sputum and/or blood culture results***

HA-MRSA or CA-MRSA pneumonia

IDSA GUIDELINES

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Clinical Infectious Diseases 2011;52(3):e18–e55

- ***IV vancomycin (A-II) or***
- ***linezolid 600 mg PO/IV twice daily (A-II) or***
- ***clindamycin 600 mg PO/IV 3 times daily (B-III), if the strain is susceptible, is recommended for 7-21 days, depending on the extent of infection.***

Pediatric considerations

IDSA GUIDELINES

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Clinical Infectious Diseases 2011;52(3):e18–e55

- ❑ *IV vancomycin is recommended*
- ❑ *clindamycin 10-13 mg/kg/dose IV every 6-8 h
(If the patient is stable without ongoing bacteremia or intravascular infection)*
- ❑ *Linezolid 600 mg PO/IV twice daily for children >12 years of age and 10 mg/kg/dose every 8 h for children <12 years of age is an alternative (A-II).*

MRSA infections of the CNS

Meningitis & CNS shunt infection

IDSA GUIDELINES

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Clinical Infectious Diseases 2011;52(3):e18–e55

IV vancomycin for 2 weeks is recommended (B-II).

Some experts recommend the addition of rifampin 600 mg daily or 300-450 mg twice daily (B-III).

***✓ Alternatives include the following:
linezolid 600 mg PO/IV twice daily (B-II)
Or
TMP-SMX 5 mg/kg/dose IV every 8-12 h
(C-III).***

MRSA infections of the CNS

**Brain abscess,
subdural empyema,
spinal epidural abscess**

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Clinical Infectious Diseases 2011;52(3):e18–e55

IV vancomycin for 4-6 weeks is recommended (B-II).

Some experts recommend the addition of rifampin 600 mg daily or 300-450 mg twice daily (B-III).

**❖ Alternatives include the following:
linezolid 600 mg PO/IV twice daily (B-II)
and
TMP-SMX 5 mg/kg/dose IV every 8-12 h
(C-III).**

MRSA infections of the CNS

Septic Thrombosis of Cavernous or Dural Venous Sinus

IDSA GUIDELINES

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Clinical Infectious Diseases 2011;52(3):e18–e55

Surgical evaluation for incision and drainage of contiguous sites of infection or abscess is recommended whenever possible (A-II).

The role of anticoagulation is controversial. IV vancomycin for 4-6 weeks is recommended (B-II).

Some experts recommend the addition of rifampin 600 mg daily or 300-450 mg twice daily (B-III).

**➤ *Alternatives include the following:
linezolid 600 mg PO/IV twice daily (B-II)
and
TMP-SMX 5 mg/kg/dose IV every 8-12 h
(C-III).***

MRSA bacteremia and infective endocarditis

Linezolid use in endovascular infections with MRSA including endocarditis has yielded inconsistent results, and guidelines have not listed linezolid as suggested therapy for MRSA endocarditis

Vancomycin-Resistant Enterococci

Linezolid has been shown to be effective for treatment of infection with vancomycin-resistant enterococci.

Successful treatment of bacteremia, endocarditis, peritoneal dialysis-related infections, osteomyelitis, endophthalmitis, ventriculitis, meningitis, intraabdominal infections, and urinary tract infections has been reported, although failures have occurred.

dose adjustment

- No dose adjustment has been suggested for patients with renal or hepatic insufficiency*
- but as linezolid and its metabolites are removed by dialysis, administration after hemodialysis is suggested.*
- Similarly, continuous renal replacement therapies also remove linezolid, but no routine change in dosage has been definitively recommended.*

drug-drug interactions

Linezolid & rifampin :

When administered to healthy volunteers in combination with rifampin, a 32% decrease in its AUC was observed.

Linezolid & Levothyroxine :

Levothyroxine has resulted in reduced linezolid concentrations as well.

Linezolid & clarithromycin :

a more than threefold increase in the linezolid AUC in a patient receiving treatment for XDR M. tuberculosis.

Resistance to linezolid

common predisposing factors:

prior exposure to the drug

and

long durations of therapy

Hematologic Toxicity

Reversible myelosuppression, including pure red blood cell aplasia, pancytopenia, and especially thrombocytopenia,

Thrombocytopenia is most common

Weekly monitoring of hematologic parameters is therefore recommended, particularly for therapeutic durations exceeding 2 weeks



Effects of Vitamin B6 Therapy for Sepsis Patients with Linezolid-Associated Cytopenias: A Retrospective Study



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Septic patients who received a combination treatment of linezolid and vitamin B6 might show positive effects for linezolid-associated reductions in some hematologic parameters (RBC, Hb, and Hct). This combined treatment might also slow PLT reduction, which was more evident in patients with severe sepsis

Monoamine Oxidase Inhibition

Linezolid is a reversible, nonselective monoamine oxidase inhibitor and has been associated with the development of serotonin syndrome (fever, agitation, mental status changes, tremors) in patients receiving concurrent serotonergic agents.

Neuropathy

- *Peripheral neuropathy may begin with dysesthesias in the hands and is poorly reversible.*
- *Optic neuropathy causes gradual onset of blurring and can lead to permanent loss of useful visual acuity if the drug is not discontinued; when detected early, visual loss has generally been reversible.*
- *Peripheral neuropathy and optic nerve disorders in a phase III study of patients receiving linezolid for 10 days occurred.*

Lactic Acidosis

Lactic acidosis, including fatal cases, has been reported most commonly during prolonged durations of linezolid therapy but can develop within the first week. Prompt recognition and drug discontinuation are critical.

Age, renal insufficiency, and drug interactions associated with linezolid overexposure increase the risk.

