



# *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 <sub>90</sub> (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.*

*nosocomial pneumonia  
involving MRSA*

CLINICAL INVESTIGATIONS ANTIBIOTICS | VOLUME 124, ISSUE 5, P1789-1797,  
NOVEMBER 01, 2003

## Linezolid vs Vancomycin\*

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

Wunderink Richard G., MD, FCCP • Rello Jordi, MD, PhD • Cammarata Sue K., MD, FCCP •  
Croos-Dabrera Rodney V., PhD • Kollef Marin H., MD, FCCP

*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***

Eur J Clin Pharmacol  
DOI 10.1007/s00228-014-1775-x

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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

Yan Wang · Yamin Zou · Jiao Xie · Taotao Wang · Xiaowei Zheng ·  
Hairong He · Weihua Dong · Jianfeng Xing · Yalin Dong

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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**

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**

- ***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

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

- ❑ *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**

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**

*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**

### **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**

**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**

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

*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



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## 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.*

