

Treatment Options for MRSA Infections

<u>Recommendation</u>	The type of treatment for patients with MRSA is individualized and based on susceptibility testing. Vancomycin is still considered the drug of choice for IV treatment of MRSA infections because of extensive experience and lower cost. Other agents should be limited to reduce emergence of resistance. Linezolid may be an alternative to vancomycin in patients at risk for renal insufficiency or those who cannot tolerate vancomycin.				
<u>Brand Name</u> <u>Generic Name</u>	<u>Cubicin</u> Daptomycin	<u>Zyvox</u> Linezolid	<u>Synercid</u> Quinupristin/dalfopristin	<u>Tygacil</u> Tigecycline	<u>Vancocin</u> Vancomycin
<u>Safety</u>	-	-	-	-	-
<i>Drug Interactions</i>	May falsely elevate the PT/INR. Use caution with other drugs that may cause rhabdomyolysis	Inhibitor of MAO Potential for interaction with serotonergic agents (TCAs, SSRIs, Demerol, trazodone) and adrenergic agents (Sudafed, sympathomimetic, vasopressor) or dopaminergic agents. Tramadol increases risk of seizures. Myelosuppressive meds may increase risk of myelosuppression. Large amounts of tyramine can result in hypertension	Inhibits CYP 3A4 metabolism. May increase plasma levels and toxic effects of agents that are metabolized by this system (e.g. Zocor, Lipitor, Haldol, Versed, Norvasc)		Increased toxicity with other ototoxic or nephrotoxic drugs. Increased neuromuscular blockade with most neuromuscular blocking agents.
<i>Pregnancy/Lactation</i>	Category B (no adequate studies) Excretion in breast milk unknown	Category C Excreted in milk of lactating rats	Category B Excretion in breast milk unknown	Category D (decreased fetal weight, minor skeletal abnormalities, and increased fetal loss observed in animal studies) Excreted in milk of lactating rats (due to low bioavailability no systemic exposure in the babies were detected)	Category C Enters breast milk
<i>Look-alike</i> <i>Sound-alike ~</i> <i>(confused with)</i>		<i>Zyvox~ Vioxx, Zosyn, Zovirax</i>			IV vancomycin ~ <i>Invanz</i> vancomycin ~ vecuronium
<i>Pediatric</i>	Safety and efficacy not established	Safety and efficacy not established in patients from birth to 11 years of age. Although dosing guidelines do exist for this population	Safety and efficacy in patients <16 years of age has not been established	Safety and efficacy not established	Confirm vancomycin concentrations in neonates and children

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Elderly	Adjust dose in elderly patients who have impaired renal function	No dosage adjustment required	No dosage adjustment required	No information	Total systemic and renal clearance of vancomycin may be reduced in the elderly. Adjust dosage schedules
Renal/Hepatic Impairment	Eliminated primarily through the kidney. Adjust dose for CrCl < 30ml/min	No dosage adjustment required	No adjustment for renal impairment. Adjustment may be necessary in patients with cirrhosis but there are no exact recommendations	Adjust for severe hepatic impairment	Dosage adjusted for renal function – check serum levels regularly. May cause nephrotoxicity – use carefully in those with renal impairment
Contraindications	Hypersensitivity	Hypersensitivity	Hypersensitivity	Hypersensitivity	Hypersensitivity. Avoid use in those with previous severe hearing loss
Precautions	<ul style="list-style-type: none"> • Myopathy and increased CPK • Not for pneumonia (poor lung penetration) • Peripheral neuropathy 	<ul style="list-style-type: none"> • Myelosuppression • Lactic Acidosis • Serotonin syndrome has been reported with co-administration of serotonergic agents • Unnecessary use leads to development of resistance • Peripheral and optic neuropathy 	<ul style="list-style-type: none"> • Pain and phlebitis when infused through peripheral line • Arthralgias, myalgias, and hyperbilirubinemia 	<ul style="list-style-type: none"> • May have similar ADR's to tetracyclines (photosensitivity, pseudotumor cerebri, pancreatitis) • Permanent tooth discoloration if used during tooth development • Associated with C. difficile colitis • Use with caution following intestinal perforation (more septic shock) 	<ul style="list-style-type: none"> • Renal impairment • Ototoxicity • Concurrent nephrotoxic or ototoxic drugs
Tolerability	-	-	-	-	-
Adverse Events	Most common: HA, constipation, N/V, diarrhea, dyspepsia, injection site reaction, insomnia, rash. Also: ↑ LFTs, limb pain, arthralgia, myopathy, ↑CPK (DC if >10x ULN)	Most common: Diarrhea, N/V. Also: reversible thrombocytopenia with prolonged therapy, ↑ LFTs, leukopenia, taste alteration, tongue discoloration, Myelosuppression	Hyperbilirubinemia, Inflammation at infusion site (42%), arthralgia (47%), myalgia (47%), headache, hyperglycemia, thrombophlebitis	Most common: Nausea (30%), Vomiting (20%) May have ADR's similar to tetracyclines: photosensitivity, pseudotumor cerebri, pancreatitis	Hypotension, flushing, red man syndrome, chills, drug fever, eosinophilia, interstitial nephritis, ototoxicity, renal failure, vasculitis, neutropenia

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Efficacy	=	+	-	=	+
FDA-approved Indications	<p>Complicated skin structure infections caused by susceptible strains of gram+ organisms: <i>S. aureus</i> (MSSA & MRSA), <i>S. pyogenes</i>, <i>S. agalactiae</i>, <i>S. dysgalactiae</i>, <i>equismilis</i>, <i>E. faecalis</i> (vancomycin susceptible strains only)</p> <p>Bacteremia, including those with right-sided infective endocarditis: <i>S. aureus</i> (MSSA & MRSA)</p> <p>Not for CAP (incidence of death and serious cardiorespiratory adverse events were increased) Does not penetrate lung tissue and is inactivated by surfactant</p>	<p>VREF infections including cases with concurrent bacteremia</p> <p>Nosocomial pneumonia: <i>S. aureus</i> (MRSA & MSSA) or <i>S. pneumoniae</i> (including MDRSP)</p> <p>Complicated skin and skin-structure infections including diabetic foot ulcerations without osteomyelitis: <i>S. aureus</i> (MSSA & MRSA), <i>S. pyogenes</i> and <i>S. galactiae</i></p> <p>Uncomplicated skin and skin-structure infections: <i>S. aureus</i> (MSSA only) or <i>S. pyogenes</i></p> <p>CAP: <i>S. pneumoniae</i> (including MDRSP), including cases with concurrent bacteremia, <i>S. aureus</i> (MSSA)</p>	<p>Life threatening infections: vancomycin resistant <i>Enterococcus faecium</i> (VREF) bacteremia</p> <p>Complicated skin and skin structure infections: <i>S. aureus</i> (MSSA), <i>S. pyogenes</i></p> <p>Not indicated for MRSA but has been used clinically</p>	<p>Complicated skin and skin structure infections: <i>E. coli</i>, <i>E. faecalis</i> (vancomycin susceptible strains only), <i>S. aureus</i> (MSSA & MRSA), <i>S. agalactiae</i>, <i>S. anginosus</i> group, <i>S. pyogenes</i>, <i>B. fragilis</i></p> <p>Complicated intra-abdominal infections: <i>C. freunii</i>, <i>E. cloacae</i>, <i>E. coli</i>, <i>K. oxytoca</i>, <i>K. pneumoniae</i>, <i>E. faecalis</i> (vancomycin susceptible strains only), <i>S. aureus</i> (MSSA), <i>S. anginosus</i> group, <i>B. fragilis</i>, <i>B. thetaiotamicron</i>, <i>B. uniformis</i>, <i>B. vulgatus</i>, <i>C. perfringens</i>, <i>Peptostreptococcus micros</i></p>	<p>Severe infections not treatable with other antimicrobials</p> <p>Severe staphylococcal infections:</p> <ul style="list-style-type: none"> • Patients allergic to penicillin or those who cannot tolerate or who failed to respond to other drugs, including penicillins or cephalosporins • MRSA • Infections may include endocarditis, bone, lower respiratory tract, septicemia, and skin and skin structure <p>Endocarditis: <i>Staphylococcus spp.</i>, <i>S. veridans</i>, <i>S. bovis</i>, <i>Enterococcus spp.</i></p> <p>Early-onset prosthetic valve endocarditis: <i>S. epidermidis</i>, diptheroids</p>
Pharmacology	Inhibits protein, DNA, and RNA synthesis by binding to bacterial membranes, which causes a rapid depolarization of cell membrane potential. Exhibits concentration-dependent killing	Inhibits bacterial protein synthesis. Bacteriostatic against enterococci and staphylococci and bactericidal against most strains of streptococci	Inhibits protein synthesis	Inhibits protein synthesis	Inhibits cell-wall biosynthesis. Exhibits time-dependent killing at a concentrations above 1.5mg/L with a brief post-antibiotic effect

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Studies	<p><u>Quinupristin/Dalfopristin vs. Vancomycin</u> Gram+ nosocomial pneumonia. Am J Respir Crit Care Med 2000;161:753-762. In 38 evaluable patients, the cure rate was 31% and 44.4% for quinupristin-dalfopristin and vancomycin respectively. No significant difference</p> <p><u>Tigecycline vs. Vancomycin</u> Skin infections. Clin Infect Dis. 2005;41(Suppl 5):S341-53. Clinical response rates were 79.7% with tigecycline and 81.9% with vancomycin-aztreonam (p = 0.4183). Incidence of adverse effects was similar with N/V occurring more often in the tigecycline group.</p> <p><u>Daptomycin vs. Vancomycin</u> MRSA skin and skin structure infections. Unpublished trial data – package insert. Daptomycin 4mg/kg IV once daily was compared to vancomycin 1gm IV q12h. Clinical success rates were similar. The incidence of CPK elevations was higher inpatients treated with daptomycin.</p> <p><u>Linezolid vs. Vancomycin</u></p> <ol style="list-style-type: none"> MRSA nosocomial pneumonia. Chest 2003;124:1789-1797. Retrospective analysis of two prospective, randomized, double-blind studies. Survival rates in the subset of patients with nosocomial pneumonia due to MRSA were 85% in the linezolid 600mg group and 67% in the vancomycin 1g group, both administered twice daily with aztreonam for 7 to 21 days (OR 2.2; 95% CI 1.0 – 4.8; p = 0.05). Clinical cure rates were 59 and 35.5%, respectively, for the MRSA subset patients (OR 3.3; 95% CI 1.3 – 8.3; p = 0.01). MRSA surgical site infections. Am J Surg 2004;188:760-6. Of those with confirmed MRSA, patients receiving linezolid had a higher microbiological cure rate than those receiving vancomycin (87 vs. 48%, respectively; p=0.0022). However, overall clinical cure rates were achieved in a similar proportion of patients with proven or suspected MRSA surgical-site infections receiving either linezolid 600mg IV or PO twice daily or vancomycin 1g twice daily (93 vs 87%, respectively; p = 0.3563). Clinical cure rates are more clinically significant than microbiological cure rates. MRSA pneumonia and skin infections. Clin Infect Dis 2002;34:1481-90. Among evaluable MRSA patients, clinical cure rates were 73.2% in the linezolid 600mg IV or PO group and 73.1% in the vancomycin 1g IV twice daily group, both administered for at least 7 days (p = 0.99). Microbiological cure rates were also similar between the groups. 				
Price	-	-	-	-	+
Usual Dose	4mg/kg q24h for 7-14days	600mg IV/PO q12h for 10 -14 days	7.5mg/kg IV q12h for 7days or longer	Initial dose of 100mg followed by maintenance dose of 50mg q12h for 5-14days	1000mg IV q12h for 7 – 10days
Relative Acquisition Cost for treatment course	10 days, 70kg patient: \$ x16	10 days, IV: \$ x13 10days, PO: \$ x10	10 days, 70kg patient: \$ x22	10 days: \$ x9	10 days: \$
Simplicity	-	=	-	=	-
	<ul style="list-style-type: none"> Adjust dose for renal failure Infused over 30min Stable for 12 hours RT Monitor CPK weekly DC Statin therapy Once daily dosing 	<ul style="list-style-type: none"> Tab and susp. PO dosage forms 100% bioavailable – easy conversion between PO and IV forms Many drug interactions IV form available in a pre-mix Administer over 30-120min 	<ul style="list-style-type: none"> Inhibitor of CYP450 3A4 – many drug interactions Must be diluted in at least 250ml to avoid venous irritation Stable for 5 hours at RT 	<ul style="list-style-type: none"> Infused over 30 – 60min. Stable up to 6h at RT No adjustment for renal failure – may need adjustment in severe liver failure 	<ul style="list-style-type: none"> Infused over 90min Must be diluted in at least 250ml Adjusted for renal function Levels must be monitored. Individualized dosing