

Antimicrobial Stewardship Backgrounder

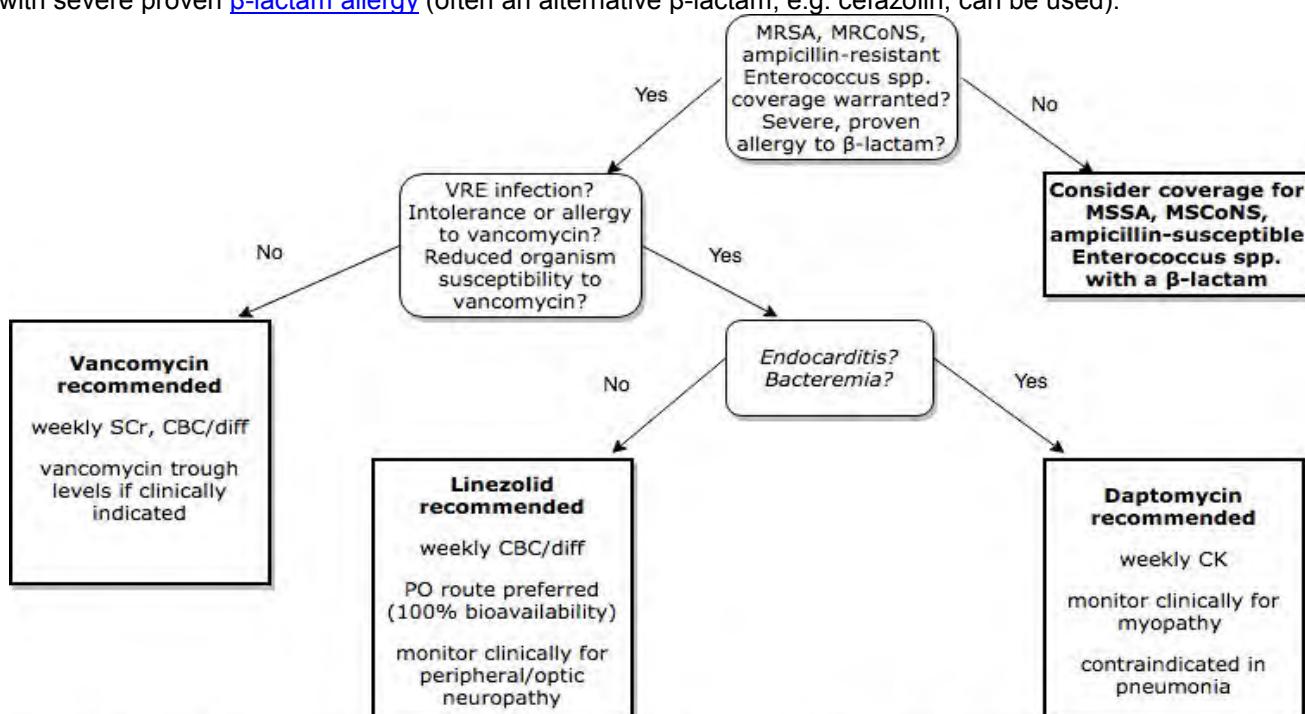
Gram positive agents: Vancomycin, Linezolid, and Daptomycin

BOTTOM LINE:

- **Vancomycin** is the recommended first-line agent for the treatment of β -lactam-resistant Gram positive organisms, excluding vancomycin-resistant Enterococcus (VRE)
- Reserve **linezolid** for vancomycin-allergic or intolerant patients, and most VRE infections
- Reserve **daptomycin** for the treatment of bacteremia and endocarditis due to β -lactam-resistant organisms in vancomycin-allergic or intolerant patients

Place in Therapy

These three agents should be reserved for therapy of β -lactam-resistant organisms or as alternatives for patients with severe proven β -lactam allergy (often an alternative β -lactam, e.g. cefazolin, can be used):



MRSA = methicillin-resistant *Staphylococcus aureus*; MRCoNS = methicillin-resistant coagulase-negative *Staphylococcus* spp.; MSSA = methicillin-susceptible *Staphylococcus aureus*; MSCoNS = methicillin-susceptible coagulase-negative *Staphylococcus* spp.; SCr = serum creatinine; CBC/diff = complete blood count and differential; CK = creatine kinase.

AHS Formulary Status & Guidelines for Use

VANCOMYCIN – formulary with guidelines:

http://webappsint.albertahealthservices.ca/Pharmacy/AHS_FORMULARY/search_details.aspx?id=2468

LINEZOLID – formulary restricted with guidelines:

http://webappsint.albertahealthservices.ca/Pharmacy/AHS_FORMULARY/search_details.aspx?id=2474

DAPTO MYCIN – formulary restricted with guidelines:

http://webappsint.albertahealthservices.ca/Pharmacy/AHS_FORMULARY/search_details.aspx?id=2464

Bactericidal vs. bacteriostatic drugs

Based on *in vitro* data, daptomycin is considered bactericidal, linezolid bacteriostatic, and vancomycin bacteriostatic against *Enterococcus* spp. and bactericidal against *Staphylococcus* spp. The clinical relevance of such distinction is questionable, with available data supporting the equivalence, and at times the superiority, of linezolid over vancomycin.¹

Central nervous system penetration: Linezolid > vancomycin > daptomycin

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Comparative clinical efficacy

Head-to-head comparisons in randomized controlled trials are only available for select MRSA infections. Linezolid has equivalent or superior clinical efficacy to vancomycin in skin/soft tissue²⁻⁴ and lower respiratory tract⁴⁻⁶ infections, although there were important limitations in some of these latter trials.⁷ Daptomycin has equivalent clinical efficacy to vancomycin in skin/soft tissue infections⁸⁻¹⁰ and bacteremia/endocarditis.¹¹ NB: Daptomycin is contraindicated in pneumonia due to inactivation of the drug by surfactant in the alveoli.

Safety

Vancomycin

Nephrotoxicity is a valid concern but can be minimized through [appropriate dosing and trough level monitoring](#), and by avoiding concurrent use of nephrotoxic drugs. Neutropenia (reversible) may occur with prolonged vancomycin use; weekly CBC/differential is recommended.

Linezolid

Reversible myelosuppression (anemia up to 29%, thrombocytopenia up to 47%, neutropenia 1-2%)¹², peripheral and optic neuropathy (<1%) are concerns with prolonged use (> 3 weeks) of linezolid. Weekly CBC/differential, and patient education for early recognition of signs and symptoms of neuropathy, are recommended. Assess for potential drug interactions with serotonergic agents, such as SSRIs or SNRIs. If concomitant therapy cannot be avoided, monitor patient for signs and symptoms of serotonin toxicity (e.g. new fever, altered mental status, clonus) for at least 3 weeks after initiation of linezolid and avoid initiation of additional serotonergic agents.¹³

Daptomycin

Dose-related, reversible myopathy and rhabdomyolysis may occur. Patient education for signs and symptoms of myopathy, plus weekly monitoring of creatine kinase (CK), are recommended.

Sustainability

After efficacy and safety, cost is a factor to be considered when choosing the optimal Gram positive agent.

In the outpatient setting, daptomycin and linezolid are a restricted benefit on the Alberta Drug Benefit List (ADBL), requiring special authorization, and must be prescribed in consultation with an Infectious Diseases specialist.

Drug costs* compared to vancomycin 15 mg/kg** IV	Inpatient		Outpatient	
	q12h	q8h	q12h	q8h
Linezolid 600 mg PO q12h	0.2	0.1	0.5	0.4
Linezolid 600 mg IV q12h	2.9	1.9	NA	NA
Daptomycin 6 mg/kg** IV daily	12.3	8.2	1.2	0.8
Daptomycin 8 mg/kg** IV daily	16.4	10.9	1.6	1.1
Daptomycin 10 mg/kg** IV daily	20.5	13.7	2.0	1.3

* Drug costs only; does not include administration or monitoring costs. Inpatient costs based on AHS contract prices; outpatient costs based on ADBL prices, March 2018.

A cost ratio < 1 indicates regimen is less expensive than vancomycin at the stated dose.

A cost ratio > 1 indicates regimen is more expensive than vancomycin at the stated dose.

** Dosages based on 75 kg patient with normal renal function. NA = not available.

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