

Antimicrobial Stewardship Backgrounder

Use of Daptomycin

BOTTOM LINE: Daptomycin should be reserved for therapy of serious Gram positive infections when first-line therapy cannot be used due to intolerance, resistance, and/or therapeutic failure.¹

Background

- Daptomycin is a cyclic lipopeptide with rapid concentration dependent bactericidal activity against many resistant Gram positive organisms.²
- **Mechanism of Action:** Binds to bacterial cell membrane (concentration- and calcium-dependent); causes rapid depolarization of the membrane, inhibiting protein, DNA, and RNA synthesis, leading to bacterial cell death.²

Spectrum of Activity³

- Daptomycin has predictable activity against most clinically important Gram positive organisms including *Staphylococcus aureus* (MSSA, MRSA, VISA, VRSA), coagulase negative staphylococci (CoNS), Enterococcus spp (including VRE), β-haemolytic streptococci (Groups A,B,C,G), *S. pneumoniae*, and viridans group streptococci.
- Daptomycin has no appreciable activity against *Listeria monocytogenes*, Gram negative organisms, or anaerobes.

Adult Dosing

Indication	Recommended Dose Given Daily (mg/kg ^{**}) ^{2,4,15}
SSTI, including DFI	4
Septic arthritis, osteomyelitis, prosthetic joint infection <i>E. faecalis</i> infections <i>S. aureus</i> bacteremia, uncomplicated*	6
Osteomyelitis, vertebral <i>S. aureus</i> bacteremia, complicated or persistent	6 – 8 8 – 10
<i>E. faecium</i> serious infections	8 – 12
<i>E. faecium</i> bacteremia, endocarditis ^{2,5}	10 – 12

SSTI = skin & skin structure infection; DFI = diabetic foot infection
* no endocarditis, no implanted prostheses, negative repeat blood cultures, defervescence within 72 hours of initiating effective therapy, and no metastatic sites of infection.

**in non-obese patients - use actual body weight to calculate the dose.

in obese patients – use dosing weight to balance efficacy and risk of muscle toxicity⁶

- Obesity defined as ABW > 20% above IBW or BMI >/=30kg/m²
- **Dosing Weight** = IBW + [0.4 x (ABW – IBW)]
 - IBW = Ideal Body Weight; ABW = Actual Body Weight

Round daptomycin dose to nearest 50 mg for doses 500 mg and greater.

Interval adjustment for daptomycin in adults with renal impairment (based on creatinine clearance)^{3,4,7,8}

≥ 30 mL/min	q24h
< 30 mL/min, hemodialysis* and CAPD	q48h
*Administer following hemodialysis on hemodialysis days CAPD = continuous ambulatory peritoneal dialysis	

Pediatric Dosing^{4,8}

Recommended dosage of daptomycin in pediatric patients with complicated skin and skin structure infections

1 to less than 2 years*	10 mg/kg q24h
2 to 6 years*	9 mg/kg q24h
7 to 11 years**	7 mg/kg q24h
12 to 17 years**	5 mg/kg q24h

Recommended dosage of daptomycin in pediatric patients with *S. aureus* bacteremia

1 to 6 years*	12 mg/kg q24h
7 to 11 years**	9 mg/kg q24h
12 to 17 years**	7 mg/kg q24h
*infuse over 60 minutes. **infuse over 30 minutes.	

Recommended dosage is for pediatric patients (1 to 17 years of age) with normal renal function. Dosage adjustment for pediatric patients with renal impairment has not been established.

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Monitoring^{4,7,8,14}

- **Creatine Kinase (CK)** at baseline and at least weekly during therapy due to risk of dose-dependent myopathy and rhabdomyolysis; monitor more frequently if on statin therapy, unexplained increases in CK, or signs of myopathy.
 - Daptomycin should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CK elevation > 1000 U/L (approximately 5 times upper limit of normal (ULN)), or in patients without reported symptoms who have marked elevations in CK (≥ 10 times ULN)^{4,8}
- **Serum Creatinine** at baseline and at least weekly – adjust dosing as needed.
- **Complete blood count & differential** at baseline and at least weekly to monitor for anemia and the potential for leukocytosis, thrombocytopenia, and eosinophilic pneumonia.
- Monitor for paresthesias, dysesthesias, muscle pain or weakness, and peripheral neuropathies.
- If diarrhea occurs, evaluate patients for *C. difficile* associated diarrhea.

Sustainability

- Daptomycin has the 7th highest inpatient antimicrobial expenditure in AHS.
[Source: DOSE Oct/21-Jun/22]
- Given that there are therapeutic and cost-effective alternatives to daptomycin, daptomycin is rarely indicated first-line and should be reserved for use according to AHS guidelines.

Prices of Select Antibiotics Relative to Vancomycin

Agent	AHS Formulary Status ^{1*}	Price Relative to Vancomycin per day ^{**}
Vancomycin 15 mg/kg IV q12h	FG	1
Linezolid 600 mg IV/PO q12h	FRG	3.6-3.7
Daptomycin 8 mg/kg [†] IV daily	FRG	7.3

* FG – Formulary with Usage Guidelines, FRG – Formulary Restricted with Usage Guidelines.

**Based on a 75kg, non-obese patient with normal renal function, and AHS contract prices as of Nov 2, 2022.

†Although 4-6 mg/kg is the recommended dose in the product monograph, higher doses of daptomycin are often used in practice either due to severity of infection, resistance to, or failure of, previous therapy.

AHS Daptomycin Guidelines¹

Daptomycin is a formulary restricted agent with the following usage guidelines:

- Therapy of serious infections (excluding pneumonia*), such as complicated skin & skin structure infections, bacteremia, and endocarditis:
 - due to Gram positive bacteria (e.g. methicillin resistant *S. aureus* (MRSA), methicillin resistant coagulase negative Staph (MRCoNS), vancomycin resistant Enterococci (VRE).
 - AND
 - used in those patients who are allergic to, or who are intolerant of, or whose infections are refractory to, or whose isolates have reduced susceptibility or resistance to, alternative formulary agents, such as vancomycin or linezolid.

***NOTE: Do NOT use daptomycin for pneumonia as the drug is inactivated by pulmonary surfactant.**

Empyema

- Daptomycin has been used successfully in the treatment of MRSA and VRE empyema.^{11,12,13}
 - Empyema forms within the pleural space where the surfactant molecules differ from alveolar pulmonary surfactant, the latter of which prevents daptomycin from being effective in the treatment of pneumonia.¹¹

Septic Pulmonary Emboli (SPE)

- Daptomycin can be used in the setting of SPE due to the vascular pathogenesis of SPE as opposed to traditional pneumonia.^{9,10,14}
 - Higher doses (≥ 8 mg/kg/dose) are recommended.¹⁰
- There should be a low threshold to adjust therapy if clinical improvement is not seen or progression of disease is noted.⁹

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