Guideline/Protocol Title	Daptomycin Standardization for Adult and Pediatric Patients Guideline
Authors	Katie Wallace, PharmD, BCPS; Donna Burgess, RPh; Thein Myint, MD; Derek Forster, MD; Sarah Cotner, PharmD, BCPS; Jeremy VanHoose, PharmD, BCPS; Amber Cordry, PharmD; Sean McTigue, MD; Joel Howard, MD; Katie Olney, PharmD, BCIDP
Committee Review	Antimicrobial Stewardship Subcommittee Pharmacy and Therapeutics Committee
Target Population	Any patient requiring therapy with daptomycin
Overview	This guideline provides evidence-based recommendations for dosing, administration, and monitoring of daptomycin
Effective Date	4/1/2016
Revised Date	3/2019 3/2021 4/2023
Expiration Date	4/2026
Schedule for Periodic Review	Every 3 years
Implementation Strategy	Pharmacists are aware of the guideline
Education Strategy	Pharmacists have been emailed the guideline and it will be shared on CareWeb and the Pharmacy SharePoint sites
Primary Outcome (s)	Percent adherence to guideline Cost savings
Outcome Assessment Plan	Review outcomes annually
Information Technology Needs	Access to CareWeb and Pharmacy SharePoint

Daptomycin Standardization for Adult and Pediatric Patients

Dosing of Daptomycin

- Doses should be calculated based on patient weight:[5-8]
  - BMI < 30 kg/m^2 - use actual body weight (ABW)
  - **BMI ≥ 30 kg/m^2 - use dosing body weight [DBW = IBW + 0.4(ABW-IBW)].**
- Doses should be rounded up to the nearest 50mg.
- Standard diluent will be 100mL normal saline.
- Pharmacists are permitted by P&T to adjust doses per this protocol.
- Daptomycin is **not** recommended for the treatment of CNS or pulmonary infections.
  - Daptomycin may still be used in patients with infective endocarditis and pulmonary septic emboli, without evidence of pneumonia.[5]
- Due to the limited number of agents available for the treatment of vancomycin-resistant *Enterococcus* (VRE), an ID consult is **strongly recommended** for VRE infections outside of the urine.

Table 1: Dose by Indication (Adults and Children ≥12 years)

Pathogen	10 mg/kg	10-12 mg/kg[#]
Staphylococcus aureus[ϕ4-13,33-36]	• Bacteremia • Right-sided endocarditis • Osteomyelitis • Septic arthritis of native joint	• Left-sided or prosthetic valve endocarditis • Foreign body/prosthetic material infection • Persistent* or complicated bacteremia
Enterococcus[14-19,33-36]		• Endocarditis • Foreign body/prosthetic material infection • *E. faecium* isolates with daptomycin MIC of ≤4** • Bacteremia • Osteomyelitis
CoNS[5,12]	• Bacteremia • Endocarditis • Foreign body/prosthetic material infection • Osteomyelitis	

Abbreviations: CoNS– coagulase-negative staphylococci; MIC– minimum inhibitory concentration; ϕDaptomycin is an alternative for treatment of MSSA in patients who are intolerant of cefazolin or nafcillin; *Persistent bacteremia defined as positive blood cultures for ≥5 days; **The CLSI breakpoint for susceptible dose-dependent (SDD) was recently updated to include all *E. faecium* isolates with an MIC ≤4 and is based on a dosage regimen of 8-12 mg/kg every 24 hours[20]

Table 2: Pediatric Dose by Age (Children <12 years)*

Indication	Age	Dose[ϕ]
Bacteremia[21,22,42] **Osteomyelitis**[22,23,42] **SSTI**[24,42]	<2 months	6 mg/kg/dose every 12 hours *Consultation with antimicrobial stewardship strongly recommended*
	≥2 months to <1 year	12 mg/kg/dose every 24 hours
	≥1 year to ≤6 years	12 mg/kg/dose every 24 hours
	≥7 years to <12 years	10 mg/kg/dose every 24 hours

*Please see **Table 1** for more detailed guidance on dosing in pediatric patients ≥12 years of age. ϕFor patients ≤7 years of age, infuse daptomycin dose over 60 minutes; for patients ≥7 years of age infuse daptomycin dose over 30 minutes[21]**. Higher-than-recommended doses of daptomycin may be required for children with sepsis to ensure appropriate exposure[22-24]**.

HealthCare

Table 3: Dose Adjustment for Renal Function

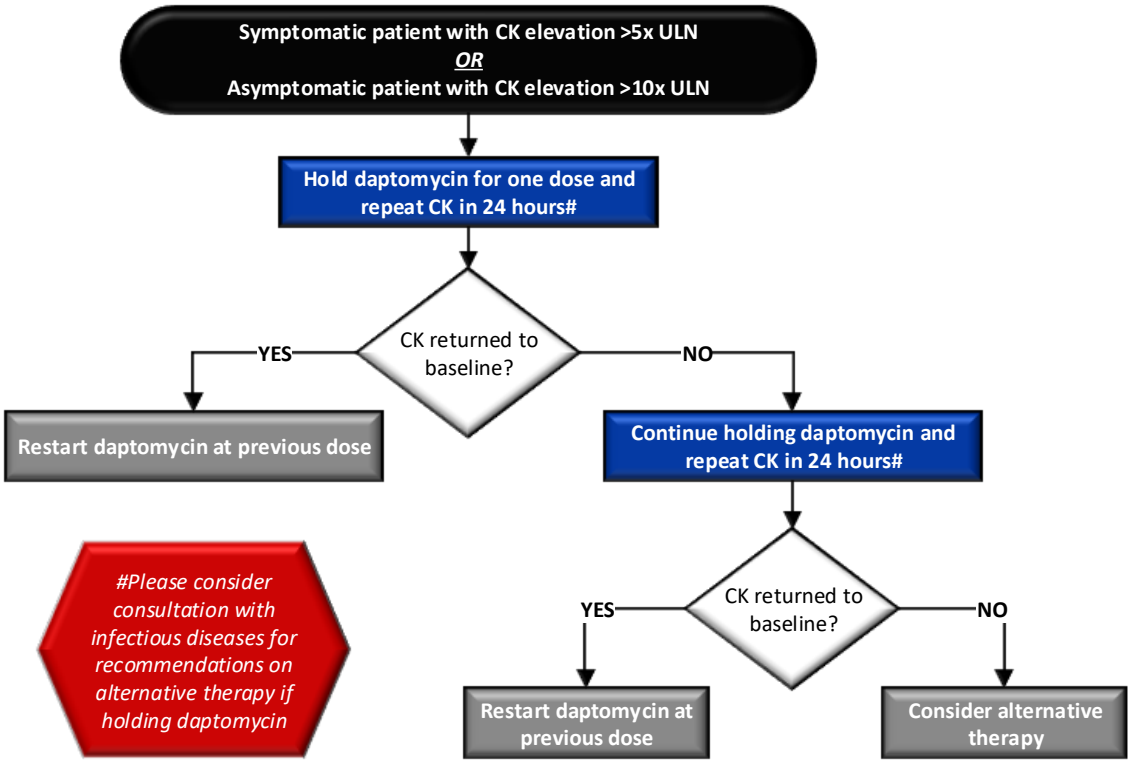
Creatinine Clearance (CrCl)	Dosing			
≥ 30 ml/min	Usual dose (Table 1) administered every 24 hours			
< 30 ml/min	Usual dose (Table 1) administered every 48 hours			
Hemodialysis[25-28] ***Inpatient**: Doses administered POST-HD* ***Outpatient**: Doses administered POST-HD or INTRA-HD (during last 30 minutes of dialysis)*	Non-HD Dose (dosed every 24 hours)	HD Day 1 (48 hr interdialytic period)	HD Day 2 (48 hr interdialytic period)	HD Day 3 (72 hr interdialytic period)
	Usual dose 10 mg/kg	10 mg/kg [a]	10 mg/kg [a]	12* mg/kg [a]
	Usual dose 12 mg/kg	12 mg/kg [a]	12 mg/kg [a]	12* mg/kg [a]
CRRT[29-32,43, 46]	8-12 mg/kg every 24 hours depending upon effluent flow			
Peritoneal Dialysis[41, 44-45]	6-10 mg/kg every 48 hours[a,b]			

*****Increasing the parent dose by 50% intra- or post-HD provides comparable AUC_{48-72} values, while maintaining acceptable trough concentration (C_{min}) values[27]. Doses ≥12 mg/kg administered in the 72-hour interdialytic period have previously been associated with increased probability (>10%) of C_{min} >24.3 mg/L. A C_{min} of ≥24.3 mg/L has been associated with increased risk (50%) of CK elevation in individuals with CrCl >30 mL/min receiving daptomycin dosed every 24 hours[28,40]. **a:** Twice-weekly monitoring of CK is recommended for all inpatients on hemodialysis or peritoneal dialysis. **b**: There is a lack of data for daptomycin dosing in peritoneal dialysis, and clinical judgement is required based on disease state, pathogen and specific peritoneal dialysis regimen. Consider an ID consult in cases of VRE bacteremia where the benefit of higher doses may outweigh the risk.

Monitoring

- The current practice of creatinine kinase (CK) monitoring at baseline and weekly thereafter should continue and may be ordered by pharmacy as part of therapeutic drug monitoring
- If patient is maintained on a statin or has CrCl <30 ml/min, consider monitoring CK twice weekly[32-33].
- Twice-weekly monitoring of CK is recommended for all patients on peritoneal dialysis or hemodialysis.
- Daptomycin should be held (**Figure 1**) in the setting of:
    - CK elevation >5x the upper limit of normal (ULN) in patients who are symptomatic
    - CK elevation >10x the ULN in patients who are asymptomatic

Figure 1: Dose Adjustment in Setting of Elevated Creatinine Kinase (CK)



Timing of Administration

When possible, preferential timing (below) should be given to standardize batching compounds in alignment of due times in an effort to decrease wasting of daptomycin IV preparations.

- First doses of daptomycin will be ordered as STAT and administered immediately (day 1)
- Subsequent doses will be rescheduled by pharmacy to 21:00 using the schedule below:
    - Initial dose given 00:01-09:00, second dose given at 21:00 that evening (day1)
    - Initial dose given 09:01-17:00, second dose given at 09:00 the next day (day2), then at 21:00 later that day (day 2)
    - Initial dose given 17:01-00:00, second dose given at 21:00 the next day (day2)

Time of first dose (day 1)	Second dose	Third dose
00:01-09:00 day 1	21:00 day 1	21:00 day 2
09:01-17:00 day 1	09:00 day 2	21:00 day 2
17:01-00:00 day 1	21:00 day 2	21:00 day 3

References

1. Ng JK, Schulz LT, Rose WE, et al. Daptomycin dosing based on ideal body weight versus actual body weight: comparison of clinical outcomes. *Antimicrob Agents Chemother* 2014;58(1):88-93.
2. Pai, M. P., & Bearden, D. T. (2007). Antimicrobial Dosing Considerations in Obese Adult Patients. *Pharmacotherapy*, 27(8), 1081–1091.
3. Dvorchik BH, Dampousse MS. The pharmacokinetics of daptomycin in moderately obese, morbidly obese, and matched nonobese subjects. *J Clin Pharmacol* 2005;45(1):48-56.
4. Ross JL, Rankin S, Marshik P, et al. Antimicrobial stewardship intervention and feedback to infectious diseases specialists: a case study in high-dose daptomycin. *Antibiotics* 2015;4:309-320.
5. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis is adults: diagnosis, antimicrobial therapy, and management complications. *Circulation* 2015;132:00-00.
6. Lawson W, Nathwani D, Eckmann C, et al. Weight-based antibiotic dosing in a real-world European study of complicated skin and soft-tissue infections due to methicillin-resistant *Staphylococcus aureus*. *Clin Microbiol Infect* 2015;21:S40-S46.
7. Shaw GJ, Meunier JM, Korfhagen J. Randomized controlled noninferiority trial comparing daptomycin to vancomycin for the treatment of complicated skin and skin structure infection in an observation unit. *J Emerg Med* 2015;49(6):928-36.
8. Murray KP, Zhao JJ, Davis SL. Early use of daptomycin versus vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: a matched cohort study. *Clin Infect Dis* 2013;56(11):1652-9.
9. Moore CL, Osaki-Kiyan P, Haque NZ, et al. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant *Staphylococcus aureus* with a high vancomycin minimum inhibitory concentration: a case-control study. *Clin Infect Dis* 2012;54(1):51-8.
10. Fowler VG, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med* 2006;355:653-65.
11. Murray BE, Arias CA, Nannini EC. Glycopeptides (vancomycin and tecoplanin), streptogramin (quinupristin-dalfopristin), lipopeptides (daptomycin), and lipoglycopeptides (televancin). In: *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* 8th ed. Bennett JE, Dolin R, Blaser MJ, eds. Philadelphia, PA.: Elsevier; 2015.
12. Seaton RA, Menichetti F, Dalekos G. Evaluation of effectiveness and safety of high-dose daptomycin: results from patients included in the Euroean Cubicin® outcomes registry and experience. *Adv Ther*2015;32:1192-1205.
13. Barber KE, Werth BJ, Rybak MJ. The combination of ceftaroline plus daptomycin allows for therapeutic de-escalation and daptomycin sparing against MRSA. *J Antimicrob Chemother* 2015 Feb;70(2):505-9.
14. Casapao AM, Kullar R, Davis SL, et al. Multicenter study of high-dose daptomycin for treatment of enterococcal infections. *Antimicrob Agents Chemother* 2013;57(9):4190-6.
15. Lubbert C, Rodloff AC, Hamed K. Real-world treatment of enterococcal infections with daptomycin: insights from a large European registry (EU-CORE). *Infect Dise Ther* 2015;4:259-271.
16. Heintz BH, Halilovic J, Christensen CL. Vancomycin-resistant enterococcal urinary tract infections. *Pharmacotherapy* 2010;30(11):1136-49.
17. Fisher L, North D. Effectiveness of low-dose daptomycin in the treatment of vancomycin-resistant enterococcal urinary tract infections. *Int J Antimicrob Agents* 2009;33(5):493-4.
18. Britt NS, Potter EM, Patel N, et al. Comparative Effectiveness and Safety of Standard-, Medium-, and High-Dose Daptomycin Strategies for the Treatment of Vancomycin-Resistant Enterococcal Bacteremia Among Veterans Affairs Patients. *Clin Infect Dis* 2017;64(5):605-13.
19. Chuang YC, Lin HY, Chen PY, et al. Effect of Daptomycin Dose on the Outcome of Vancomycin-Resistant. Daptomycin-Susceptible *Enterococcus faecium* Bacteremia. *Clin Infect Dis* 2017;64(8):1026-34.
20. CLSI M100-ED30: 2020 Performance Standards for Antimicrobial Susceptibility Testing, 30th Edition.
21. Arrieta, A., MD, et al. Randomized Multicenter Study Comparing Safety and Efficacy of Daptomycin Versus Standard-of-care in Pediatric Patients with Staphylococcal Bacteremia. *Pediatric Infectious Disease Journal*. Vol 37, Number 9, September 2018.
22. Antachopoulos C, Ilia S, Kadiltzoglou P, Baira E, Dokoumetzidis A, Gikas E, Volakli E, Sdougka M, Briassoulis G, Roilides E. Pharmacokinetics of Daptomycin in Critically Ill Pediatric Patients. *Antimicrobial Agents and Chemotherapy.* May 2018, 62 (6) e02462-17; DOI: 10.1128/AAC.02462-17
23. Bradley JS, Arrieta AC, Digtyar VA, Popejoy MW, Grandhi A, Bokesch P, Hershberger E, Dorr MB, Tan CM, Murata Y, Wolf DJ, Bensaci M. Daptomycin for Pediatric Gram-Positive Acute Hematogenous Osteomyelitis. *Pediatr Infect Dis J.* 2020 Sep;39(9):814-823.
24. Bradley J, Glasser C, Patino H, Arnold SR, Arrieta A, Congeni B, Daum RS, Kojaoghlanian T, Yoon M, Anastasiou D, Wolf DJ, Bokesch P. Daptomycin for Complicated Skin Infections: A Randomized Trial. *Pediatrics.* Mar 2017, 139 (3) e20162477.
25. Haselden M, Leach M, Bohm N. Daptomycin dosing strategies in patients receiving thrice-weekly intermittent hemodialysis. *Ann Pharmacother* 2013;47(10):1342-7.
26. Salama NN, Segal JH, Churchwell MD, et al. Single-dose daptomycin pharmacokinetics in chronic haemodialysis patients. *Nephrol Dial Transplant* 2010;25(4):1279-84.
27. Butterfield JM[1], Mueller BA, Patel N, et al. Daptomycin pharmacokinetics and pharmacodynamics in a pooled sample of patients receiving thrice-weekly hemodialysis. *Antimicrob Agents Chemother* 2013;57(2):864-72.
28. Patel N, Cardone K, Grabe DW, et al. Use of pharmacokinetic and pharmacodynamics principles to determine optimal administration of daptomycin in patients receiving standardized thrice-weekly hemodialysis. *Antimicrob Agents Chemother* 2011;55(4):1677-83.
29. Seaton, R. Andrew, et al. "Evaluation of effectiveness and safety of high-dose daptomycin: results from patients included in the European Cubicin® outcomes registry and experience." *Advances in therapy* 32.12 (2015): 1192-1205..
30. Presiwerk B, Rudiger A, Fehr J. Experience with daptomycin daily dosing in ICU patients undergoing continuous renal replacement therapy. *Infection* 2013;41:5530557.
31. Feifan X, Sanwang L, Zeneng C. Population pharmacokinetics and dosing considerations of daptomycin in critically ill patients undergoing continuous renal replacement therapy. *Journal of Antimicrobial Chemotherapy.* 75 (2020): 6; 1559–1566.
32. Soraluce, A., et al. "Population pharmacokinetics of daptomycin in critically ill patients." International journal of antimicrobial agents 52.2 (2018): 158-165.
33. Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. *Circulation*. 2015;132(15):1435-1486.

34. Kullar R, McClellan I, Geriak M, et al. Efficacy and safety of daptomycin in patients with renal impairment: a multicenter retrospective analysis. *Pharmacotherapy* 2014;34(6):582-9.
35. Berg ML, Estes LL, Dierkhising RA, et al. Evaluation of impact of statin use on development of CPK elevation during daptomycin therapy. *Ann Pharmaother* 2014;48:320-37.
36. Timbrook, T.T., Caffrey, A.R., Luther, M.K., Lopes, V. and LaPlante, K.L. (2018), Association of Higher Daptomycin Dose (7 mg/kg or Greater) with Improved Survival in Patients with Methicillin-Resistant Staphylococcus aureus Bacteremia. Pharmacotherapy, 38: 189-196.
37. Cervera C, Castañeda X, Pericas JM, Del Río A, de la Maria CG, Mestres C, Falces C, Marco F, Moreno A, Miró JM. Clinical utility of daptomycin in infective endocarditis caused by Gram-positive cocci. *Int J Antimicrob Agents*. 2011 Nov;38(5):365-70.
38. Turnidge J, Kahlmeter G, Cantón R, MacGowan A, Giske CG. Daptomycin in the treatment of enterococcal bloodstream infections and endocarditis: a EUCAST position paper. *Clinical Microbiology and Infection*. 26 (2020) 1039e10431040.
39. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis*. 2011;1-38.
40. Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. Daptomycin exposure and the probability of elevations in the creatinine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. *Clin Infect Dis*. 2010;50:1568-1574.
41. Benziger DP, Pertel PE, Donovan J, et al. Pharmacokinetics and safety of multiple doses of daptomycin 6 mg/kg in noninfected adults undergoing hemodialysis or continuous ambulatory peritoneal dialysis. *Clin Nephrol*. 2011;75(1):63-69.
42. Wei, X., Zhao, M., Li, X., & Xiao, X. (2020). Pharmacokinetic/Pharmacodynamic Analysis of Daptomycin Against Staphylococcus aureus and Enterococcus faecium in Pediatric Patients by Monte Carlo Simulation. *The Journal of Clinical Pharmacology.* 60(6), 768–774. doi:10.1002/jcph.1576.
43. Preiswerk B, Rudiger A, Fehr J, Corti N. Experience with daptomycin daily dosing in ICU patients undergoing continuous renal replacement therapy. *Infection*. 2013 Apr;41(2):553-7.
44. Cardone KE, Lodise TP, Patel N, et al. Pharmacokinetics and pharmacodynamics of intravenous daptomycin during continuous ambulatory peritoneal dialysis. *Clin J Am Soc Nephrol.* 2011 May;6(5):1081-8. doi: 10.2215/CJN.08510910.
45. Benziger, David P. et al. Pharmacokinetics and safety of multiple doses of daptomycin 6 mg/kg in noninfected adults undergoing hemodialysis or continuous ambulatory peritoneal dialysis. *Clinical nephrology.* 75 1 (2011): 63-9
46. Xu X, Khadzhynov D, Peters H, Chaves RL, et al. Population pharmacokinetics of daptomycin in adult patients undergoing continuous renal replacement therapy. *Br J Clin Pharmacol*. 2017 Mar;83(3):498-509. doi: 10.1111/bcp.13131.