UWHC Guidelines for the Use of Daptomycin (Cubicin®)

Guidelines developed by: Antimicrobial Use Subcommittee; UWHC Drug Policy Program (DPP)
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Originally Approved by P&T Committee: July 2010
Updated: February 2011
Scheduled For Review: February 2013

A. Background
Antimicrobial resistance among Gram-positive organisms, particularly the sharply rising incidence of life-threatening infections caused by methicillin-resistant staphylococci (MRSA) and vancomycin-resistant enterococci (VRE), has become a major concern. New antimicrobial drugs that are effective against these organisms are available; however, to preserve their utility, minimize their unique toxicities and provide cost-effective therapy, it is essential to ensure that these newer agents are used selectively and appropriately.

Daptomycin (Cubicin®, Cubist Pharmaceuticals) is the first antibiotic in the new cyclic lipopeptide class. It is bactericidal in a concentration-dependent manner against a wide variety of Gram-positive organisms, including those resistant to vancomycin.

B. Appropriate Indications
Appropriate use of daptomycin for extended therapy will usually require a culture/susceptibility test with identification of an organism that exhibits resistance to other possible antimicrobial agents. Based on the potential for bacterial resistance associated with the use of daptomycin, the UW Pharmacy and Therapeutics Committee has approved its use in the following conditions:

1.0 For patients with bacteremia with suspected MRSA, (i.e., coagulase-positive gram-positive cocci in a blood culture with identification and sensitivities not yet completed) with daptomycin dosed at 6 mg/kg. Step-down therapy to vancomycin should usually be made if the vancomycin MIC of the organism is ≤1.5 mcg/mL. Under certain circumstances approved by Infectious Diseases, daptomycin may be continued unless the vancomycin MIC is ≤1.0 mcg/mL, usually in more serious staphylococcal infections.

2.0 Life-threatening infection, usually septic shock, endocarditis, complex deep skin and soft tissue infections (SSTIs) or intraabdominal sepsis, where there is strong suspicion that the patient is infected by MRSA or VRE (e.g., the patient is known to have been or is currently colonized by these organisms). If the cultures do not confirm MRSA or VRE infection within 72 hours, daptomycin should be switched to vancomycin or other antibiotics.

3.0 Invasive infections caused by vancomycin-resistant Enterococcus faecium such as bacteremia, intraabdominal infection, or deep SSTIs.

4.0 SSTIs or osteomyelitis caused by MRSA with a vancomycin MIC >1.5 mcg/mL. Under certain circumstances approved by Infectious Diseases, daptomycin may be continued unless the vancomycin MIC is ≤1.0 mcg/mL.

5.0 Other MRSA/VRE indications:

5.1 Unable to tolerate vancomycin therapy. Combination therapy may be warranted if gram-negative organisms are present. A history of vancomycin “red man syndrome” (the histamine-release reaction) should generally not be considered a reason to use daptomycin for primary treatment; in that circumstance,
pretreatment with an H1-histamine blocker, such as diphenhydramine, and slowing the infusion rate can allow vancomycin to be used safely.

5.2 When the infecting MRSA strain is known to have a vancomycin MIC >1.5 mcg/mL.

5.3 Single-dose procedural prophylaxis in patients known to be colonized with VRE or with an MRSA isolate with vancomycin MIC ≥2.0 mcg/mL, in a normally sterile body site undergoing an invasive interventional radiology or surgical procedure of that site (dose =4 mg/kg).

C. Inappropriate Uses

1.0 Daptomycin should not be used to treat pneumonia.

2.0 Daptomycin should not be used for empiric therapy of non-life-threatening infections where there is little evidence that MRSA or VRE are infecting or colonizing microorganisms.

3.0 Daptomycin should generally not be used for treating coagulase-negative staphylococcal infections where vancomycin is the drug of choice. Daptomycin may be considered if the vancomycin MIC is ≥4 mcg/mL.

4.0 Daptomycin should not be used for inpatients for the simple convenience of once-daily dosing. (except for transition of patients on vancomycin to daptomycin at or near the time of discharge to facilitate once-daily outpatient therapy).

5.0 Daptomycin should not be used to treat asymptomatic catheter or non catheter-associated bacteriuria.

6.0 MSSA infections, unless there are serious reactions to all appropriate beta-lactams, and the vancomycin MIC is >1.5 mcg/mL, or concomitant serious adverse reaction to vancomycin.

7.0 Under most circumstances, SSTIS or osteomyelitis with MRSA where the vancomycin MIC is ≤ 1.5 mcg/mL.

8.0 Antimicrobial prophylaxis for surgical procedures in patients colonized with MRSA, in the absence of a severe vancomycin allergy.

D. Contraindications

1.0 Daptomycin is contraindicated in any person with a known hypersensitivity to daptomycin or any of the product components.

E. Precautions

1.0 Concomitant use of daptomycin and HMG-CoA reductase inhibitors may increase the risk of the development of myopathy. HMG-CoA inhibitors may be considered for temporary suspension.

2.0 The use of antimicrobial agents may promote the overgrowth of nonsusceptible organisms. Appropriate measures should be taken if superinfection occurs during the course of treatment.

3.0 Development of diarrhea following administration of daptomycin may indicate the complicating pseudomembranous colitis.
4.0 Dose adjustment is required in renal insufficiency. Patients with creatinine clearances of less than 30 mL/min should receive the normal dose, but the dosing interval should be increased to once every 48 hours.

5.0 Avoid using except in cases of strongly suspected or documented infection to reduce the development of resistant organisms.

F. Adverse Effects / Drug Interactions
1.0 Daptomycin has been associated with myalgia, increased creatine kinase and rhabdomyolysis.

2.0 Gastrointestinal side effects associated with daptomycin in clinical trials may include diarrhea, nausea, constipation and vomiting.

3.0 Other side effects observed in clinical trials (> 2% of patients) include headache, insomnia, rash, dizziness and fever.

4.0 Less common side effects in clinical trials (at least 1% of patients) include hypotension, pruritus, rash, hyperkalemia, hypokalemia, anemia, increased liver function tests, dizziness, headache, insomnia, renal failure, dyspnea and fungal infection.

5.0 Therapeutic levels of daptomycin may falsely prolong prothrombin time and elevate INR. If abnormal results are obtained, a specimen should be drawn just prior to the next daptomycin dose and tested for PT/INR. If the results are still abnormal, further investigation as to the cause is warranted.

G. Monitoring Parameters/Documentation
1.0 Therapeutic
   1.1 Culture and susceptibility of pathogen from site of infection
   1.2 White blood cell count with differential
   1.3 Physical exam to monitor for resolution of signs/symptoms of infection

2.0 Toxic
   2.1 CBC and blood chemistry periodically
   2.2 Baseline serum CPK and recheck at least weekly while on therapy

H. Infectious Disease Authorization
1.0 Use of daptomycin generally requires approval by Infectious Diseases.

2.0 The physician wishing to prescribe daptomycin for an adult patient will contact pager #3333 between the hours of 0700 and 2200 to reach the ID physician on call. If ID approval is given, the ordering physician will then inform the unit pharmacist that approval has been given. A formal consult is not required, but the prescribing physician or the pharmacist should document the name of the authorizing Infectious Diseases physician in the appropriate questions field when entering the order into HealthLink.

3.0 The physician wishing to prescribe daptomycin for a pediatric patient will contact the Pediatric Infectious Disease physician on call between the hours of 0700 and 2200 for approval of the order for daptomycin. If ID approval is given, the ordering physician will then inform the unit pharmacist that approval has been given. A
formal consult is not required, but the prescribing physician or the pharmacist should document the name of the authorizing Infectious Diseases physician in the appropriate questions field when entering the order into HealthLink.

4.0 In the event of an emergency or if there is an expected delay in the approval process, such as an order written between 2200 and 0700, a single dose of drug may be dispensed, if the appropriate criteria for treatment are met, by the Pharmacy without ID approval. Subsequent doses will not be dispensed until ID approval has been obtained.

I. Dose and Administration

1.0 Doses of daptomycin are administered every 24 hours and should be based on ideal body weight (IBW) to reduce the risk of myopathy.

2.0 If the dose entered is not based on IBW, the pharmacist is authorized to change the dose to one based on IBW unless the prescriber indicates “Dose as written” or the Infectious Diseases physician’s note indicates that the dose is to be based on a weight other than IBW.

3.0 If patient’s actual body weight is less than IBW (ABW < IBW), dose based on ABW.

4.0 For MRSA and MSSA bacteremia, endocarditis, 6 mg/kg, based on IBW, for 2-6 weeks.

5.0 Vancomycin-resistant Enterococcus faecium infections involving bacteremia: 6 mg/kg IV, based on IBW, every 24 hours for up to 14 consecutive days.

6.0 Vancomycin-resistant Enterococcus faecium infections NOT with bacteremia, such as urinary tract infections and SSTIs: 4 mg/kg IV, based on IBW, every 24 hours for up to 14 days.

7.0 Shorter courses of therapy (i.e., 3-7 days) may be suitable for other types of infections. Complicated skin and skin structure infections due to MRSA may be treated with 4 mg/kg, based on IBW, IV every 24 hours for a maximum of 8 to 10 consecutive days.

8.0 Doses greater than 6 mg/kg, based on IBW, are not recommended at this time. In unusual circumstances, larger doses may rarely be indicated. Practitioners requesting the use of larger doses must get authorization through the #3333 pager.

9.0 Dosing during inpatient hemodialysis is 4mg/kg after HD for SSTIs or 6 mg/kg after HD for bloodstream infections. For inpatients, doses are given after the patient returns from HD.

10.0 For outpatients receiving HD, a 20% increase (~1mg/kg) may be given during the last 30 minutes of each HD session (5 mg/kg or 7 mg/kg). A dose increase on the HD session prior to 68 hour intra-dialytic period (Friday on a Monday, Wednesday, Friday schedule or Saturday on a Tuesday, Thursday, Saturday schedule) is NOT necessary but may be prescribed at the physicians discretion. Alternative dosing, see #13.

11.0 Patients receiving HD with residual renal function (≥ 100ml in 24 hours) should strongly be considered for an increased dose (50%) before an inter-dialytic period greater than 48 hours (ie. 4/4/6 or 6/6/9).
12.0 Dosing during continuous veno-venous hemodialysis (CVVHD) is 8mg/kg every 48 hours or 4mg/kg every 24 hours. Both regimens yield similar AUC/MIC ratios (PK/PD characteristic associated with efficacy) at steady-state; however, the 8mg/kg dose lower minimum concentration (PK parameter associated with safety). Dosing in alternative continuous renal replacement therapies has not been studied.

13.0 Daptomycin injection should be administered over a period of 30 minutes. Do not use the intravenous infusion bag in series connections. Concomitant drugs should be administered separately. Diluents containing dextrose should not be used.

14.0 In the outpatient setting, a two-minute infusion may be used and is preferred.

15.0 The IV line should be flushed before administration of any other medications.

16.0 **Important Note:** Daptomycin may take 60 – 90 minutes to prepare due to the amount of time it takes to go into solution. Therefore, a STAT dose may not be available for 90 minutes or longer after the order is entered.

### J. Cost

1.0 Cost* comparison of linezolid, quinupristin/dalfopristin, daptomycin and vancomycin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route, Dose</th>
<th>Cost/Day ($)</th>
<th>Cost/14 Days ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daptomycin</td>
<td>4 mg/kg IBW IV Q24h</td>
<td>122.06 per 65 kg</td>
<td>1708.84 per 65 kg</td>
</tr>
<tr>
<td></td>
<td>6 mg/kg IBW IV Q24h</td>
<td>183.09 per 65 kg</td>
<td>2563.34 per 65 kg</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1 g IV Q12h</td>
<td>8.12</td>
<td>113.62</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg IV Q12h</td>
<td>192.34</td>
<td>2692.76</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg PO Q12h</td>
<td>148.12</td>
<td>2073.68</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg IV Q12h x 7 days plus 600 mg PO Q12h x 7 days</td>
<td>170.23</td>
<td>23.83.22</td>
</tr>
<tr>
<td>Quinupristin / Dalfopristin</td>
<td>500 mg IV Q8h</td>
<td>456.99</td>
<td>6397.86</td>
</tr>
</tbody>
</table>

*Costs current as of 1/11/11
K. References


5.0 Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: Data from a randomized trial of patients with bacteremia and endocarditis. *Clin Infect Dis* 2010;50:1568-1574.

