Daptomycin Dosing in Obesity: Which weight is the right weight?

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Abstract # 12
IRB Approved

1. Describe concerns regarding daptomycin use in obese patients that could impact safety and efficacy of the drug.

2. Identify patients who might benefit from adjusted body weight (AdjBW) dosing of daptomycin based on the results of this study.

Study Institution
- 350-bed academic medical center
- Level 1 trauma center
- Infectious diseases section with ID specialists and fellows

In 2014, OU Medical Center approved a protocol to dose daptomycin based on AdjBW in patients with body mass index (BMI) ≥ 30 kg/m²

BMI = Body mass index

Disclosure Statement
- Ashley N. Fox, PharmD
- Potential Conflicts of Interest: None
- Sponsorship: None
- Proprietary information or results of ongoing research may be subject to different interpretations
- Speaker’s presentation is educational in nature and indicates agreement to abide by the non-commercialism guidelines provided

Pre-Assessment Questions
1. Which of the following adverse effects have occurred more commonly in obese patients taking daptomycin?
   A. Seizures
   B. Increased creatine phosphokinase
   C. Thrombocytopenia

2. At what BMI would you consider dosing daptomycin with an adjusted body weight?
   A. BMI ≥ 30 kg/m²
   B. BMI 18.5 - 25 kg/m²
   C. BMI 25 - 30 kg/m²

Learning Objectives

Daptomycin Overview and Activity in Obesity
- Concentration dependent, bactericidal activity against most gram-positive bacteria – MRSA and VRE
- Pharmacokinetic parameter associated with efficacy: AUC/MIC
- In a pharmacokinetic study comparing obese patients to non-obese controls dosed with actual body weight (ABW)
  - AUC increased ~ 30%
  - Cmax increased ~ 30%

Higher daptomycin exposure in obese patients

Daptomycin Use in Obesity

- Daptomycin received FDA approval with doses studied of 4-6 mg/kg/day ABW in patients with normal renal function.
- When approved, limited data was available for dosing in obese patients.
- Retrospective studies suggest increased adverse drug events (creatine phosphokinase elevations) in populations with:
  - Obesity (BMI ≥ 30 kg/m²)
  - Concomitant statin therapy

References:

Daptomycin Dosing in Obesity

- Ng, et al., 2014
  - Retrospective review
  - Actual body weight (ABW) vs. ideal body weight (IBW) in patients with BMI ≥ 30 kg/m²
  - Staphylococcus aureus, Enterococcus, CONS
  - Variety of infections
  - No difference in clinical success or adverse events

- Bookstaver, et al., 2013
  - Retrospective review
  - Daptomycin dosed with ABW in patients with BMI ≥ 30 kg/m²
  - Stratified by BMI Classification
  - No difference in ADEs between BMI classifications
  - No difference in clinical effectiveness

CONS = Coagulase negative staph. sp.
ADE = Adverse drug event
ULN = Upper limit of normal

Secondary Endpoints

- Microbiologic success
- Mortality at 90 days
- Readmission within 90 days
- Combined safety endpoint
  - Creatine phosphokinase (CPK) elevation
  - Patient reported myopathy
  - Rhabdomyolysis

Definitions

- Clinical Failure
  - Development of resistance as noted on subsequent culture results
  - Recurrent signs or symptoms of infection necessitating antibiotic therapy modification as documented in the patient’s electronic medical record

- Microbiologic Success
  - At least 1 documented culture showing microbiologic eradication and no evidence of subsequent clinical failure

- Creatine phosphokinase (CPK) elevation
  - No CPK elevations at baseline or no CPK checked at baseline followed by CPK elevations ≥ 3x upper limit of normal (ULN)
  - Baseline CPK greater than the ULN followed by CPK elevations ≥ 5x ULN
  - Or daptomycin stopped by the treating physician due to concern for CPK elevation

- Rhabdomyolysis
  - Documented rhabdomyolysis on admission (secondary to trauma admission, seizure activity, or volume depletion)
  - Elevation in CPK concentration as defined above PLUS
    - Positive urine myoglobin
    - Or acute kidney injury
Methodology

- Retrospective chart review
- Approved by University of Oklahoma HSC IRB
- Identified patients by daptomycin order and BMI
- Evaluation of daptomycin dosing in separate cohorts
  - AdjBW: January 2014 - December 2015
  - ABW: January 2012 - December 2013
- Data collected utilizing a standardized form
  - Demographic data and daptomycin indication/dosing
  - Efficacy data: Clinical and microbiologic success
  - Safety data: rhabdomyolysis, CPK elevation, and patient reported myalgias
- Statistical analysis
  - Descriptive statistics (Fisher’s exact, Mann-Whitney U test, Chi square)
  - Multivariate logistic regression

Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>• Adult patients &gt; 18 years</td>
<td>• Renal dysfunction</td>
</tr>
<tr>
<td>• BMI ≥ 30 kg/m²</td>
<td>• CRCl &lt; 30 mL/min</td>
</tr>
<tr>
<td>• Daptomycin duration of therapy &gt; 72 hours</td>
<td>• QRBH dosing</td>
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<tr>
<td></td>
<td>• CRRT or HD</td>
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<tr>
<td></td>
<td>• Daptomycin therapy prior to admission</td>
</tr>
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<td></td>
<td>• Isolates not susceptible to daptomycin</td>
</tr>
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<td></td>
<td>• Infections with retained hardware</td>
</tr>
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<td></td>
<td>• Patients with rhabdomyolysis on admission</td>
</tr>
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<td></td>
<td>• Variations of documented weight of ≥ 20% during admission</td>
</tr>
</tbody>
</table>

Interim Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ABW Cohort (n=30)</th>
<th>AdjBW Cohort (n=26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Median (IQR)</td>
<td>47 (32-53)</td>
<td>51 (42-58)</td>
<td>0.2971</td>
</tr>
<tr>
<td>Female</td>
<td>60 (18)</td>
<td>42 (11)</td>
<td>0.1864</td>
</tr>
<tr>
<td>BMI Class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Class I (30-34.9 kg/m²):</td>
<td>47 (14)</td>
<td>47 (14)</td>
<td>0.3103</td>
</tr>
<tr>
<td>- Class II (35-39.9 kg/m²):</td>
<td>27 (8)</td>
<td>35 (9)</td>
<td></td>
</tr>
<tr>
<td>- Class III (&gt;40 kg/m²):</td>
<td>27 (8)</td>
<td>38 (10)</td>
<td></td>
</tr>
<tr>
<td>BMI Median (IQR)</td>
<td>35 (32-43)</td>
<td>37 (34-41)</td>
<td>0.3503</td>
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<tr>
<td>Doses</td>
<td></td>
<td></td>
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<tr>
<td>- 4.5-5.5 mg/kg/day</td>
<td>13 (4)</td>
<td>19 (5)</td>
<td></td>
</tr>
<tr>
<td>- 5.6-7.49 mg/kg/day</td>
<td>70 (21)</td>
<td>15 (4)</td>
<td>0.0093</td>
</tr>
<tr>
<td>- ≥ 7.5 mg/kg/day</td>
<td>17 (5)</td>
<td>65 (17)</td>
<td></td>
</tr>
<tr>
<td>Concurrent statin therapy</td>
<td>23 (7)</td>
<td>12 (3)</td>
<td>0.3102</td>
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Limitations

- Retrospective, single center trial
- Small sample size
- No statistical power calculation
- Microbiological success dependent upon repeated cultures from primary site of infection with demonstrated clearance
- Admissions related to primary infection at OSH not captured by medical record
- Weights obtained for antibiotic dosing may not be uniform (bed weight versus standing weights)
Conclusions

- Interim data suggests there is no difference in clinical failure or adverse effects when patients are dosed using an adjusted body weight.
- Secondary endpoints regarding microbiological cure, mortality at 90 days and readmission within 90 days were not statistically different between the groups.
- Daptomycin doses have increased in clinical practice.
  - This project could provide clinical and safety information for patients with obesity and high dose daptomycin.

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Self-Assessment Question

1. For which of the following patients could the data presented assist in determining the daptomycin dosing strategy?

A. 29 YO M with BMI 38 kg/m$^2$, CrCl of 98 mL/min, and surgical site infection with retained hardware
B. 75 YO M with BMI 32 kg/m$^2$, CrCl < 30 mL/min, and diagnosis of VRE bacteremia
C. 60 YO M with BMI of 28 kg/m$^2$, CrCl of 85 mL/min, and diagnosis of VRE intra-abdominal abscess
D. 45 YO F with BMI of 45 kg/m$^2$, CrCl of 55 mL/min, and diagnosis of osteomyelitis