High-Dose Daptomycin for Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infections: Muscle vs. Microbe

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Objectives:

- Define prevalence, morbidity, and mortality associated with *Staphylococcus aureus* infections
- Describe agents available for management of *S. aureus* bacteremia and complications
- Evaluate evidence with high dose daptomycin and its effects on microbiological and clinical success rates
- Interpret potential toxicity and tolerability issues associated with high dose daptomycin
I. **Staphylococcus aureus**
   A. Major cause of both health care-associated and community acquired infections\(^1\)-\(^4\)
      1. Most frequently occurring bacterial pathogen in hospitalized inpatients
      2. Second most prevalent bacterial pathogen among clinical isolates in outpatients\(^2\)-\(^4\)
   B. Ability to invade and cause disease in previously normal tissue at virtually all sites\(^5\)
      1. Common manifestations include skin and soft tissue, respiratory, bone, joint, and endovascular infections

II. **S. aureus** bacteremia (SAB)
   A. Epidemiology
      1. Incidence of SAB, particularly methicillin-resistant strains (MRSA), has dramatically increased in recent years\(^2\)-\(^4\)
         a. Most common cause of nosocomial bacteremia in North America and Latin America\(^2\)
            i. Responsible for 26% of all bloodstream infections in 24,179 patients in nationwide surveillance study (1999-2002)
            ii. Incidence of 10.3 bloodstream infections per 10,000 patient admissions
      2. Reasons for increased incidence\(^5\)-\(^7\)
         a. Increased use of intravascular devices
         b. Increased frequency of invasive surgery
         c. Intravenous (IV) injection drug use
         d. Immunosuppression
            i. HIV/AIDS epidemic
            ii. Transplantation
   B. Complications of SAB
      1. Infective endocarditis (IE)
         a. Most common pathogen causing IE\(^7\),\(^8\)
            i. Frequency is 25-32% in patients with SAB
         b. Associated with higher mortality compared to other organisms\(^8\)
      2. Metastatic infections
         a. One-third of patients will develop as a result of hematogenous seeding\(^3\),\(^9\),\(^10\)
         b. Common sites\(^4\),\(^7\)
            i. Bone and joints
            ii. Epidural space and intervertebral discs
            iii. Heart valves (native)
            iv. Pulmonary
            v. Intra-abdominal organs
               a. Splenic, hepatic, or kidney abscesses
         c. Suppurative collections at these sites serve as potential foci for recurrent infections
      3. Prosthetic device infection\(^11\)
         a. 12-23% cultures yield S. aureus
         b. Surgical debridement necessary as part of treatment
   C. Morbidity and mortality of SAB
      1. High morbidity and mortality even with appropriate treatment\(^4\),\(^7\),\(^9\)
         a. Overall mortality rate from SAB ranges from 11-43%
      2. Two meta-analyses examined mortality with methicillin susceptible S. aureus (MSSA) and MRSA bacteremia\(^13\),\(^14\)
         a. MRSA associated with increased risk of death compared to MSSA
            i. Potential explanations
a. Virulence
b. Underlying comorbidities
c. Decreased therapeutic options and efficacy
d. Delay in initiation of appropriate therapy
   1. Associated with an almost 2-fold increase in mortality\textsuperscript{15}
b. 23.4\% mortality associated with MSSA vs. 36.4\% with MRSA (p<0.001; confidence interval [CI], 1.25-1.63)\textsuperscript{13}
   i. 31 studies, 3,963 patients with SAB
D. Non-pharmacologic management of MRSA bacteremia
   1. Believe the blood culture
      a. Pien et al\textsuperscript{5} found that 93\% of blood cultures with \textit{S. aureus} were true bloodstream infections (BSI)
      i. Only 1\% \textit{S. aureus} blood cultures were ultimately contaminants
      ii. 6\% were of unknown significance
   2. Find the source
      a. Identification of infected sites is critically important\textsuperscript{4,9,12}
         i. Physical exam
         ii. Radiographic imaging studies
         iii. Echocardiography
            a. New murmur?
   3. Eliminate the problem
      a. Infection recurrence rates strongly associated with failure to eliminate source\textsuperscript{4,8-10}
         i. Incision and drainage
         ii. Removal of intravenous catheters
            a. Most common cause of bacteremia – 23\% of episodes\textsuperscript{5}
            b. Septic thrombophlebitis
         iii. Consideration of early valve replacement
   4. Bad things happen without source control
      a. Hardware removal\textsuperscript{16}
         i. 56\% of 23 patients who failed to have infected hardware removed relapsed despite long course of treatment
            a. Only 16\% of 221 patients with device removal experienced recurrence (p<0.1)
      b. Patients with permanent pacemakers or implantable cardiac defibrillators and SAB are at an increased risk of recurrent bacteremia or death if not removed\textsuperscript{17}
      c. Surgical management of \textit{S. aureus} endocarditis
         i. Medical treatment unless established criteria for surgical indication met\textsuperscript{18,19}
            a. Congestive heart failure
            b. Myocardial invasion
            c. High risk for embolic complications
            d. Failure to respond to antimicrobial therapy
         ii. Patients with \textit{S. aureus} endocarditis are likely to benefit from early surgical intervention\textsuperscript{19-21}
            a. 252 patients with IE had improved short and long term survival rates with early surgical intervention before completion of antibiotics (p = 0.04)\textsuperscript{19}
   5. Not all bloodstream infections are created equal
      a. Risk factors for development of complications\textsuperscript{10,12}
         i. Persistent bacteremia
            a. Defined as 72-96 hours after appropriate antibiotic initiation
b. Strongest indicator of clinical complication
   ii. Community acquired
   iii. Skin lesions suggestive of metastasis (<7% of cases)
   iv. Persistent fevers

III. Antimicrobial management of MRSA bacteremia
    A. Duration of antimicrobial therapy
       1. At least 14 days of treatment\textsuperscript{12}
          a. Meta-analysis of 11 pooled studies addressed efficacy of short-course therapy (≤ 14 days) for catheter-associated SAB
             i. Rate of late complications was 6.1% (95% CI, 2.0%-10.2%)
       2. Infectious Diseases Society of America (IDSA) – Intravascular catheter-related treatment guidelines\textsuperscript{23}
          a. 14-day course of therapy
             i. Endocarditis exclusion with transesophageal echocardiography (TEE)
             ii. No implanted prostheses
             iii. Follow-up cultures drawn 48-96 hours after initial blood cultures negative
             iv. Patient without fever within 72 hours of appropriate therapy
             v. No signs or symptoms of localizing metastatic staphylococcal infection
          b. 4-6 week course of therapy
             i. Complications or serious underlying diseases
    B. Antibacterials available for management

Table 1: Therapeutic options for MRSA Bacteremia in 2010\textsuperscript{12}

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Established efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin (IV)</td>
<td>Cell wall synthesis inhibitor</td>
<td>“Red man” syndrome, neutropenia, thrombocytopenia, nephrotoxicity?</td>
<td>Therapeutic drug monitoring, reports of increase in failures with increased MIC</td>
</tr>
<tr>
<td></td>
<td>Bactericidal</td>
<td></td>
<td>UHS: $12.28/1 g</td>
</tr>
<tr>
<td>Daptomycin (IV)</td>
<td>Cell membrane depolarizer via Ca\textsuperscript{2+} dependent pathway</td>
<td>CPK level elevation</td>
<td>Increase in daptomycin MIC during therapy</td>
</tr>
<tr>
<td></td>
<td>Bactericidal</td>
<td></td>
<td>UHS: $228.24/500 mg</td>
</tr>
<tr>
<td><strong>Salvage therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid (IV and PO)</td>
<td>Protein synthesis inhibitor</td>
<td>Bone marrow suppression, irreversible sensory motor polyneuropathy, serotonin syndrome</td>
<td>Not studied well for long-term use, increased monitoring warranted, especially &gt;28 days</td>
</tr>
<tr>
<td></td>
<td>Bacteriostatic</td>
<td></td>
<td>UHS: $186.36/day</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin (IV)</td>
<td>Protein synthesis inhibitor</td>
<td>Myalgia and arthralgia, pain/inflammation at infusion site, thrombophlebitis</td>
<td>Unfavorable safety profile, requires central access, expensive</td>
</tr>
<tr>
<td></td>
<td>Bactericidal</td>
<td></td>
<td>UHS: $465.27/day</td>
</tr>
<tr>
<td>TMP/SMZ (IV and PO)</td>
<td>Inhibition of bacterial folic acid pathway</td>
<td></td>
<td>Limited to less severe infections, outpatient treatment</td>
</tr>
<tr>
<td></td>
<td>Bactericidal</td>
<td>Rash, hypersensitivity reactions</td>
<td>UHS: $21.40 (IV on backorder)</td>
</tr>
</tbody>
</table>
C. Vancomycin

1. Mainstay treatment choice for MRSA infections for over 40 years
   a. Relative lack of clinical experience with newer agents compared to vancomycin
   b. Head-to-head registration studies with newer agents, including ceftaroline and telavancin, failed to demonstrate clear superiority over vancomycin
   c. Much lower acquisition cost for vancomycin compared to newer agents

2. Issues with vancomycin
   a. Heteroresistant MRSA (h-VISA)
      i. Subpopulations of S. aureus isolates have MICs for vancomycin with reduced susceptibility (4-32 µg/mL)
      ii. Associated with high bacterial load and initially low serum vancomycin levels
      iii. Method for detection not available in clinical microbiology laboratories
   b. Controversial “MIC creep”
      i. Single center data demonstrated an increase in vancomycin MICs in S. aureus between 2000-2005
         a. Shift from ≤0.5 to 1 µg/mL by broth microdilution method (70.4% vs. 19.9%; p<0.01)
      ii. Data from SENTRY Antimicrobial Surveillance Program between 1997-2003 show true resistance to vancomycin remains rare and has stable prevalence among staphylococci
   c. Increased failures with increased MIC
      i. Reports of vancomycin treatment failure with susceptible isolates have increased in the past decade
      ii. Clinical Laboratories Standards Institute (CLSI) decreased vancomycin susceptibility breakpoint to ≤2 µg/mL in 2006
      iii. Studies by Hidayat et al, Soriano et al, and Lodise et al suggest increased MICs associated with treatment failures
         a. Empiric therapy with vancomycin and MIC of 2 µg/mL was an independent predictor of increased mortality
         b. High vancomycin trough concentrations (15-20 µg/mL) may not lead to better outcomes
   d. Nephrotoxicity
      i. Limited data suggesting a direct relationship between toxicity and specific serum vancomycin concentrations
         a. Conflicting data and inability to standardize for confounding nephrotoxic agents
         b. Patient population variety
         c. Safety of high troughs over a prolonged period has not been studied
   e. Therapeutic monitoring of vancomycin in adult patients – consensus review of ASHP, IDSA, and SIDP
      i. Troughs are the most accurate and practical method for monitoring efficacy (Evidence level: IIB)
         a. Should be maintained > 10 mg/L (Evidence level: IIIB)
         b. 15-20 mg/L for complicated infections (AUC/MIC ≥ 400) (Evidence level: IIIB)
      ii. Monitoring trough serum concentrations best suited to reduce nephrotoxicity in aggressive dosing (Evidence level: IIB)
D. Daptomycin35-37
   1. MIC for susceptibility is ≤1 µg/mL for *S. aureus*
      a. MICs for intermediate susceptibility or resistance have not been determined
   2. FDA-approved indications
      a. Complicated skin and skin structure infections (cSSSI) caused by susceptible gram-positive strains - 4 mg/kg/day for 7-14 days38
      b. SAB and right-sided IE - 6 mg/kg/day for 14-42 days39
      c. Not indicated for treatment of pneumonia40
   3. Mechanism of action
      a. Cyclic lipopeptide which contains a water-soluble hydrophilic core with lipophilic tail
      b. Binds cell membrane via calcium-dependent insertion of lipid tail, forming an ion-conduction structure that rapidly depolarizes the cell membrane via an efflux of potassium
         i. Disruption of DNA, RNA, and protein synthesis leading to cellular death
   4. Pharmacokinetics36
      a. Linear pharmacokinetics at doses up to 12 mg/kg/day
      b. Limited volume of distribution
         i. 0.09 L/kg
         ii. Highly protein bound (91-96%)
      c. Renally excreted – dosage adjustment warranted (every 48 hours)
      d. Obese patients41,42
         i. Dose based on total body weight
         ii. Risk of under treating serious infections by dosing based on lean body weight vs. potential reduction in less frequent muscle related adverse effects
   5. Discovered in the early 1980’s by Eli Lilly and Company
      a. Development and investigational efforts halted in 1991
         i. Concerns about skeletal muscle toxicity at dosages as low as 6 mg/kg/day with twice daily dosing
         ii. Animal studies demonstrated daptomycin-induced myopathy is specific to skeletal muscle, distinct from other myopathies, and readily reversible43
   6. Cubist Pharmaceuticals resumed work with daptomycin and introduced it in clinical trials in 1999
      a. Skeletal muscle effects related to dosing interval rather than peak drug concentration (C_{Max}) or area under the curve (AUC)43
      b. Absence of rhabdomyolysis was demonstrated with doses up to 75 mg/kg/day in dogs
7. New concern
   a. Eosinophilic pneumonia (EP)
      i. Product label lists pulmonary eosinophilia as post-marketing adverse event
      ii. U.S. and non-U.S. reports of EP in patients treated with daptomycin submitted to the FDA Adverse Events Reporting System (AERS) from 2004-2010
      iii. Multiple case reports in literature
         iv. EP etiology hypothesized to be a result of daptomycin’s ability to bind lung surfactant causing accumulation and concentrations high enough to injure epithelium and cause inflammation

IV. Preliminary in vitro study with daptomycin and vancomycin
   A. Bactericidal activity of daptomycin and vancomycin evaluated against MRSA in an in vitro pharmacokinetic/pharmacodynamic (PK/PD) infection model with simulated endocardial vegetations (SEV)
      1. Simulated regimens of daptomycin 6 (D6) and 10 mg/kg/day (D10) - MIC 1.0 µg/mL
         a. Broth supplemented with 4 g/dL albumin, 25 mg/L Ca²⁺, and 12.5 mg/L Mg²⁺
      2. Vancomycin 1 g BID (V) - MIC 0.5 µg/mL

Figure 1: Daily serum creatine phosphokinase (CPK) activities in dogs

Figure 2: Time-kill curve comparing various regimens of daptomycin to vancomycin
V. Daptomycin versus standard therapy

Study


Objective

- Compare safety and efficacy of daptomycin vs. standard therapy for S. aureus bacteremia and endocarditis

Design

- Noninferiority, open-label, prospective, randomized trial conducted between August 2002 and February 2005
- Patient selection:
  - Inclusion: ≥18 y/o with presumed S. aureus bacteremia
  - Exclusion: CrCl ≤30 mL/min, osteomyelitis, polymicrobial bacteremia, pneumonia
- Primary outcome - clinical success at the test-of-cure (TOC) visit (42 days post treatment)
- Regimen:
  - Daptomycin 6 mg/kg IV Q24H
  - Standard therapy with vancomycin 1 g IV Q12H or antistaphylococcal penicillin 2 g Q4H, both with gentamicin 1 mg/kg Q8H X 4 days
- Definitions:
  - Uncomplicated bacteremia: Isolation of S. aureus from enrollment blood cultures in patients without endocarditis and evidence of hematogenous spread
    - Duration: minimum of 10-14 days
  - Complicated bacteremia: Isolation of S. aureus from blood cultures ≥2 days through study day 5, spread of infection, or infection involving prostheses not removed within 4 days
    - Duration: 28-42 days
  - Endocarditis: Duke’s criteria
  - Failure: clinical failure, microbiologic failure, death, failure to obtain blood culture, receipt of potentially effective nonstudy antibiotics, premature discontinuation of study medication, or adverse event

Statistics

- Populations: Intention-to-treat (ITT), modified intention-to-treat (MITT), per-protocol
- Assuming 65% efficacy, power of 80%, one-sided α=0.025, 90 patients required to test null hypothesis (treatments differed by at least 20%)
- 95% CI, χ²

Results

- Demographic characteristics and risk factors for S. aureus infection for MITT population were similar at baseline
  - Exception: more HIV positive patients in daptomycin group vs. standard therapy group
- 235 randomized:
  - 120 to daptomycin
  - 115 to standard therapy: 62 to antistaphylococcal penicillin, 53 to vancomycin

<table>
<thead>
<tr>
<th>Final Diagnosis</th>
<th>Daptomycin (n=120)</th>
<th>Standard Therapy (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated bacteremia</td>
<td>32 (26.7%)</td>
<td>29 (25.2%)</td>
</tr>
<tr>
<td>Complicated bacteremia</td>
<td>60 (50%)</td>
<td>61 (53%)</td>
</tr>
<tr>
<td>Uncomplicated RSIE*</td>
<td>6 (5%)</td>
<td>4 (3.5%)</td>
</tr>
<tr>
<td>Complicated RSIE*</td>
<td>13 (10.8%)</td>
<td>12 (10.4%)</td>
</tr>
<tr>
<td>LSIE**</td>
<td>9 (7.5%)</td>
<td>9 (7.8%)</td>
</tr>
</tbody>
</table>

*Right-sided infective endocarditis
**Left-sided infective endocarditis

- Primary outcome: 53/120 (44.2%) with daptomycin vs. 48/115 (41.7%) with standard therapy

<table>
<thead>
<tr>
<th>Susceptibility</th>
<th>Daptomycin</th>
<th>Standard Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>33/74 (44.6%)</td>
<td>34/70 (48.6%)</td>
</tr>
<tr>
<td>MRSA</td>
<td>20/45 (44.4%)</td>
<td>14/44 (31.8%)</td>
</tr>
</tbody>
</table>

- Median length of time to clearance of bacteremia
  - MRSA: 8 days with daptomycin, 9 days with vancomycin
MSSA: 4 days with daptomycin, 3 days with antistaphylococcal penicillin

<table>
<thead>
<tr>
<th>Reason for failure</th>
<th>Daptomycin (N=120)</th>
<th>Standard Therapy (N=115)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>67 (55.8%)</td>
<td>67 (58.3%)</td>
<td></td>
</tr>
<tr>
<td>Microbiologic failure, clinical failure, or both</td>
<td>23 (19.2%)</td>
<td>15 (13.0%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Microbiologic failure</td>
<td>23 (19.2%)</td>
<td>11 (9.6%)*</td>
<td>0.17</td>
</tr>
<tr>
<td>Clinical failure without microbiologic failure</td>
<td>4 (3.3%)</td>
<td>4 (3.5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Adverse event</td>
<td>8 (6.7%)</td>
<td>17 (14.8%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Receipt of nonstudy antibiotics that could have influenced outcome</td>
<td>20 (16.7%)</td>
<td>16 (13.9%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Death</td>
<td>13 (10.8%)</td>
<td>13 (11.3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>No blood culture obtained</td>
<td>9 (7.5%)</td>
<td>12 (10.4%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Patient could not be evaluated</td>
<td>9 (7.5%)</td>
<td>14 (12.2%)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*9 in vancomycin group and 2 in antistaphylococcal penicillin group

- Failures with daptomycin were more frequently associated with persistent and relapsing infection
- Daptomycin MIC increased from baseline in 7/120
  - 6 resulted in microbiologic failure, 5/6 were MRSA
  - MIC increased from 0.25 µg/mL (5/6) and 0.5 µg/mL (1/6) to 2.0 and 4.0 µg/mL, respectively
- 4/53 with vancomycin had MIC increase to 2 µg/mL from 0.5 or 1.0 µg/mL
- No significant association between serum levels of daptomycin or vancomycin with microbiologic failure
- Failures with standard therapy were more often associated with treatment limiting side effects
- CPK elevations: 6.7% with daptomycin vs. 0.9% with standard therapy, p=0.04
  - 3/120 treated with daptomycin discontinued treatment due to elevation
- Renal impairment
  - Standard therapy: 18.1% vs. daptomycin: 6.7%, p=0.009
  - 5/116 with standard therapy discontinued treatment due to renal impairment
  - Vancomycin + gentamicin: 20.4%, antistaphylococcal penicillin + gentamicin: 18.6%
- Mortality did not differ between treatment arms (11%)

Authors’ Conclusion
- Daptomycin is not inferior to standard therapy for the treatment of S. aureus bacteremia and right-sided endocarditis caused by MSSA or MRSA

Discussion
- Open label
- Author’s conclude persistent and relapsing infections with daptomycin were a source control issue
  - Associated with deep-seated infections and indications for surgical debridement
- Daptomycin exhibits a high degree of protein binding (91-96%)
- Time to question the dose?
VI. Cases reported involving emergence of daptomycin non-susceptibility at recommended doses for MRSA infections

Table 2: Cases reported with daptomycin MIC increase on therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex/Age</th>
<th>Co-Morbidities</th>
<th>Site of Infection</th>
<th>Previous antibiotic treatment</th>
<th>Dosage/duration of daptomycin treatment</th>
<th>Change in MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirschwerk et al</td>
<td>F/92</td>
<td>Permanent pacemaker, history of MRSA bacteremia</td>
<td>Vegetation on the pacemaker wire, bacteremia</td>
<td>Vancomycin</td>
<td>6 mg/kg/day x 28 days</td>
<td>&lt;0.75 to 2.0 µg/mL</td>
</tr>
<tr>
<td>Hayden et al</td>
<td>F/86</td>
<td>N/A</td>
<td>Prosthetic knee septic arthritis</td>
<td>Vancomycin</td>
<td>6 mg/kg/day for 22 days, then q48h x 13 days</td>
<td>0.25 to 4 µg/mL</td>
</tr>
<tr>
<td>Hayden et al</td>
<td>F/61</td>
<td>N/A</td>
<td>Sternal osteomyelitis and bacteremia</td>
<td>Vancomycin</td>
<td>6 mg/kg/day x 42 days</td>
<td>0.5 to 4 µg/mL</td>
</tr>
<tr>
<td>Mangili et al</td>
<td>M/54</td>
<td>ESLD, history of SBP, hepatic encephalopathy, variceal bleeding</td>
<td>Bacteremia, infected portal vein thrombus</td>
<td>Ceftriaxone, vancomycin</td>
<td>4 mg/kg/day x 4 days then 6 mg/kg/day x 23 days</td>
<td>&lt;1.0 to 2.0 µg/mL</td>
</tr>
<tr>
<td>Marty et al</td>
<td>M/61</td>
<td>AML, GVHD</td>
<td>Bacteremia</td>
<td>Vancomycin, gentamicin, linezolid</td>
<td>6 mg/kg/day x 28 days</td>
<td>0.5 to 2.0 µg/mL</td>
</tr>
</tbody>
</table>

VII. Back to the laboratory: in vitro model utilizing high-dose daptomycin

A. Leonard et al

1. Evaluation of traditional and high dose (HD) vancomycin and daptomycin against MRSA and hVISA in an in vitro PK/PD SEV infection model
   a. Six clinical isolates obtained

<table>
<thead>
<tr>
<th>Staphylococcus isolate</th>
<th>Daptomycin MIC (mg/L)</th>
<th>Vancomycin MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA 494</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>MRSA 67</td>
<td>0.125</td>
<td>0.5</td>
</tr>
<tr>
<td>R1720</td>
<td>0.125</td>
<td>0.5</td>
</tr>
<tr>
<td>R2295</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>R3640</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>R1629</td>
<td>0.25</td>
<td>2</td>
</tr>
</tbody>
</table>

b. Regimens evaluated over 96 hours: daptomycin 6, 10, and 12 mg/kg Q24H and vancomycin 1 and 2 g Q12H
Figure 3: Standard and high dose daptomycin vs. vancomycin against MRSA 494

2. Results
   a. Vancomycin with minimal activity against MRSA isolates and minimal to no activity against hVISA
      i. HD vancomycin without improvement except in 1/6 isolates (MRSA)
      ii. Small elevations in MICs observed in hVISA isolates with both dosing regimens
   b. Daptomycin was bactericidal to detection limits against all isolates
      i. Superior to standard and high dose vancomycin (p < 0.001)
         a. No MIC changes were observed
VIII. Safety and tolerability with high dose daptomycin


Objective  
- Assess multiple-dose pharmacokinetic (PK) profile and linearity of daptomycin in healthy volunteers at doses ranging from 6 to 12 mg/kg once daily
- Assess safety and tolerability at doses of 8, 10, and 12 mg/kg/day for 14 days

Design  
- Single-center, randomized, double-blind, placebo-controlled, ascending-dose phase 1 study conducted with healthy volunteers
- Inclusion: Healthy subjects, 18-45 years, body mass indexes (BMI) of 18.5-30 kg/m², normal renal function, no active medical findings
- Three cohorts:
  - Cohort 1: daptomycin 10 mg/kg (n=9) vs. placebo (n=3)
  - Cohort 2: daptomycin 12 mg/kg (n=9) vs. placebo (n=3)
  - Cohort 3: daptomycin 6 mg/kg (n=6) and 8 mg/kg (n=6) for PK baseline comparisons
- PK assessments
  - Blood samples: predose, end of infusion, and 9 other points on days 1, 4, 7, and 14
- Safety assessments were performed at baseline, during treatment, and post treatment

Results  
- Demographics were comparable among cohorts, majority of subjects Hispanic (89%)
- PK data were determined on day 1, at steady state (day 4), and on day 14
  - Plasma concentrations and AUC increased in linear fashion with dose range 6 to 12 mg/kg
- PK data from day 4 at steady state:

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Cmax (µg/mL)</th>
<th>AUC₀₋₂₄ (µg x h/mL)</th>
<th>Free AUC₀₋₂₄ (µg x h/mL)*</th>
<th>t₁/₂ (h)</th>
<th>Vd (L/kg)</th>
<th>CL (mL/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (N=6)</td>
<td>93.9 (6.0)</td>
<td>632 (78)</td>
<td>45</td>
<td>7.9 (1.0)</td>
<td>0.101 (0.007)</td>
<td>9.1 (1.5)</td>
</tr>
<tr>
<td>8 (N=6)</td>
<td>123.3 (16.0)</td>
<td>858 (213)</td>
<td>61</td>
<td>8.3 (2.2)</td>
<td>0.101 (0.013)</td>
<td>9.0 (3.0)</td>
</tr>
<tr>
<td>10 (N=9)</td>
<td>141.1 (24.0)</td>
<td>1039 (178)</td>
<td>73</td>
<td>7.9 (0.6)</td>
<td>0.098 (0.017)</td>
<td>8.8 (2.2)</td>
</tr>
<tr>
<td>12 (N=9)</td>
<td>183.7 (25.0)</td>
<td>1277 (253)</td>
<td>90</td>
<td>7.7 (1.1)</td>
<td>0.097 (0.018)</td>
<td>9.0 (2.8)</td>
</tr>
</tbody>
</table>

*Estimated based on a 93% protein binding

- Minimal drug accumulation occurs after the first dose
- Safety
  - No serious adverse effects or discontinuations due to adverse events
  - CPK levels were within normal range for all subjects throughout the treatment
    - No arthralgias or myalgias were not reported
  - Hematology, clinical chemistry, and vital-signs within normal range at all assessments

Authors’ Conclusion  
Daptomycin has linear, dose-proportional pharmacokinetics over 6 – 12 mg/kg dose range
Daptomycin well tolerated at doses up to 12 mg/kg/day for 14 days without any serious adverse events or discontinuation

Discussion  
- Good premise and logic for utilization of high-dose daptomycin
- Cannot extrapolate to clinical patient population
- Exclusion criteria strict
- Data for 14 day therapy minimal for severe MRSA infections
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>• Examine safety of daptomycin at doses &gt;6 mg/kg for courses ≥14 days in clinical practice</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>• Single center retrospective chart review evaluating patients treated with high dose daptomycin between January 2004 through April 2007&lt;br&gt;• Inclusion: Patients who received daptomycin &gt;6 mg/kg for ≥ 14 days&lt;br&gt;• Definitions:&lt;br&gt;  o Safety: adverse events documented in medical record&lt;br&gt;  ▪ Compared with adverse events listed in package insert and those documented in bloodstream infection (BSI) trial&lt;br&gt;  ▪ Graded 1-4 based on severity&lt;br&gt;  o Significant CPK elevation: 10 X increase from upper limit of normal with or without musculoskeletal symptoms&lt;br&gt;• Hospital policy required discontinuation of concomitant 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA)-reductase inhibitors&lt;br&gt;• Infections categorized as uncomplicated bloodstream infection (BSI), complicated BSI, IE, cSSSI, bone and joint, intra-abdominal, and unidentified infections</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>• 61 patients met criteria with mean age 67 years&lt;br&gt;  o Mean dose 8 mg/kg (7-11 mg/kg)&lt;br&gt;  o Median duration 25 days of therapy (14-82 days)&lt;br&gt;• Diagnosis&lt;br&gt;  o Uncomplicated BSI (n=7), complicated BSI (n=19), left-sided IE (n=6), cSSSI (n=14), bone and joint (n=9), intra-abdominal (n=5), febrile neutropenia (n=1)&lt;br&gt;• Organisms&lt;br&gt;  o MRSA (n=16), MSSA (n=2), methicillin-resistant <em>Staphylococcus epidermidis</em> (n=3), Enterococcus spp (n=18), group B streptococcus (n=1), unidentified (n=12)&lt;br&gt;• 58/61 (95.1%) had CPK evaluated&lt;br&gt;  o CPK evaluated ≤72 hours of initiation: 41/58&lt;br&gt;  o Paired CPK levels: 34/41&lt;br&gt;• 22/61 (36%) with grade 1 adverse events (anemia, diarrhea, nausea, hypokalemia, arthralgias)&lt;br&gt;  o None required discontinuation&lt;br&gt;• 3/61 (4.9%) receiving 8 mg/kg had CPK level elevations &gt;1000 U/L and were symptomatic with musculoskeletal complaints after 24-28 days of therapy&lt;br&gt;  o Resolution within one week of discontinuation</td>
</tr>
<tr>
<td><strong>Authors’ Conclusion</strong></td>
<td>Daptomycin treatment well tolerated at mean dose 8 mg/kg/day for median duration of 25 days&lt;br&gt;Incidence of symptomatic CPK elevation within range reported with lower doses of daptomycin and/or shorter treatment durations</td>
</tr>
<tr>
<td><strong>Discussion</strong></td>
<td>• Small cohort of patient&lt;br&gt;• Retrospective chart review&lt;br&gt;• Inconsistency with CPK analysis</td>
</tr>
</tbody>
</table>

**Objective**
- Evaluate the relationship between daptomycin exposure and probability of CPK elevation in patients with SAB with or without IE

**Design**
- Subset of data from Fowler et al was analyzed
- Inclusion: patients who received daptomycin 6 mg/kg once daily for 10 – 42 days and had daptomycin plasma serum levels available
- Population PK models used, Bayesian daptomycin exposures at steady state (day 5) estimated and correlated CPK levels
- PK sampling:
  - 5 serial blood samples collected on day 5 at predose, at 0.25-0.5, 1-1.5, 3-5, and 9-12 h after the infusion
- 2-compartment, open model with zero-order intravenous input and first-order elimination
  - $C_{\text{max}}$, $C_{\text{min}}$, and AUC were determined for each patient using the population-of-one utility
- Endpoints:
  - Occurrence of and time to CPK elevation during therapy to 3 days post treatment
- CPK levels were measured 3 times/week
- Monte Carlo simulation:
  - Conducted with mean parameter estimates from final population PK model and exposure-response relationships

**Statistics**
- Univariate logistic regression to evaluate relationship between day 5 exposure measures and probability of CPK elevation
- Kaplan –Meier analysis
- Cox proportional hazards regression

**Results**
- 108 patients met inclusion criteria
  - 6/108 demonstrated defined CPK elevation
  - CPK levels returned to normal range during treatment or post treatment follow-up period
  - 3/6 patients required discontinuation of daptomycin
  - $C_{\text{min}}$ when evaluated as a categorical variable, based on CART-derived breakpoint of 23.4 mg/L, was most significant parameter associated with CPK elevation ($p < .001$; odds ratio [OR], 33.0; 95% CI, 4.6-237)
  - After 14 days of therapy, the probability of CPK elevation was 0.5 and 0.025 in patients with $C_{\text{min}} \geq 24.3$ mg/L or <24.3, respectively (50% vs. 2.9%; $p=0.002$)

**Authors’ Conclusion**
- Daptomycin $C_{\text{min}} \geq 24.3$ mg/L was associated with increased probability of CPK elevation

**Discussion**
- Lack of sensitivity
- Small amount (6/108) of patients with PK data available had elevated CPK
- Only 3/6 were above the proposed $C_{\text{min}}$ breakpoint

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Weight (kg)</th>
<th>Duration (days)</th>
<th>Day 1 of elevation</th>
<th>Peak CPK</th>
<th>CPK:ULN</th>
<th>Muscle AE</th>
<th>CrCl (mL/min)</th>
<th>$C_{\text{min}}$ (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>111</td>
<td>28</td>
<td>20</td>
<td>1934</td>
<td>9.9</td>
<td>No</td>
<td>132.1</td>
<td>3.8</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>71</td>
<td>10</td>
<td>5</td>
<td>5548</td>
<td>30</td>
<td>Yes</td>
<td>106.7</td>
<td>7.5</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>121</td>
<td>28</td>
<td>14</td>
<td>895</td>
<td>5.1</td>
<td>No</td>
<td>194.2</td>
<td>8.6</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>80</td>
<td>14</td>
<td>13</td>
<td>3171</td>
<td>21.1</td>
<td>No</td>
<td>65.6</td>
<td>24.3</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>115</td>
<td>15</td>
<td>15</td>
<td>2977</td>
<td>22.1</td>
<td>Yes</td>
<td>105</td>
<td>25.64</td>
</tr>
<tr>
<td>6</td>
<td>86</td>
<td>112</td>
<td>16</td>
<td>16</td>
<td>3140</td>
<td>13.5</td>
<td>No</td>
<td>39.7</td>
<td>45.4</td>
</tr>
</tbody>
</table>

- $C_{\text{min}}$ when evaluated as a categorical variable, based on CART-derived breakpoint of 23.4 mg/L, was most significant parameter associated with CPK elevation ($p < .001$; odds ratio [OR], 33.0; 95% CI, 4.6-237)
IX. Clinical data
   A. Limited case reports describe clinical success with higher doses of daptomycin\textsuperscript{57,58}
   B. Promise with high dose
      1. Retrospective chart review evaluating clinical use of daptomycin at standard dose (SD): \( \leq 6 \text{ mg/kg/day} \) and high doses (HD): \( > 6 \text{ mg/kg/day} \) for \( \geq 10 \text{ days} \textsuperscript{59} 
         a. 53 patients met criteria
              i. SD: 22 patients, HD: 31 patients
              ii. Median treatment duration 13.5 days and 19 days for the SD and HD groups, respectively
         b. All \textit{S. aureus} isolates were susceptible to daptomycin by Etest
         c. All 53 patients underwent CPK analysis during treatment
         d. Clinical success was observed in 13/19 (68\%) and 27/29 (93\%) in the SD and HD, respectively (\( p<0.05 \))
              i. 19/22 and 27/31 MRSA isolates in the SD and HD groups, respectively
         e. Differences in CPK levels not observed between groups
              i. 1 patient in HD experienced significant grade 3 CPK level elevation (>1000 U/L)
                 a. Normalized within one week of discontinuation of daptomycin
   C. High dose does no better
      1. Semi-single blind, randomized, prospective, comparative pilot study evaluating efficacy and safety of daptomycin at 10 mg/kg/day for 4 days versus standard therapy with vancomycin or antistaphylococcal penicillin for cSSSI\textsuperscript{60}
         a. Primary efficacy end-point – response 7-14 days post treatment
         b. 100 patients randomized, 48 in each arm treated
              i. 75\% with MRSA infections
         c. Clinical success rates were 75\% (36/48) for daptomycin and 87.5\% (42/48) for comparator
              i. No statistical difference between treatment arms
              ii. 3/48 (6.3\%) experienced elevations in CPK > 500 U/L
                 a. All levels reversed and none required discontinuation

X. Summary of findings
   A. Difficulties with MRSA mainstay therapy vancomycin have left us looking for new alternatives
   B. First bacteremia study in 30+ years to result in new antibiotic indication for SAB and IE prompted high-dose daptomycin discussion
   C. Daptomycin’s concentration dependent killing and promising in vitro data suggest pushing the dose could resolve issues of resistance and improve efficacy
   D. Higher rates of clinical and microbiologic success with high-dose compared to standard dose found in retrospective review
   E. Recent studies show that although muscle toxicity is still a concern with daptomycin, it is well tolerated in high doses
XI. Conclusions
   A. Vancomycin should still be used empirically and as first line therapy for severe MRSA infections
   B. Daptomycin is a viable alternative to vancomycin for MRSA bloodstream infection and IE in a limited population
      1. Persistent bacteremia despite adequate source control and therapeutic vancomycin concentrations\textsuperscript{23}
      2. Vancomycin MIC of 2 µg/mL or less in the setting of worsening clinical picture
      3. Known vancomycin MIC >2 µg/mL or recent failure on vancomycin\textsuperscript{30}
   C. High dose daptomycin should be used in place of standard dosing for severe MRSA infections
   D. Not recommended in patients with known or suspected pneumonia or central nervous system infection\textsuperscript{40}
   E. Dosing based on total body weight\textsuperscript{41,42}
      1. Risk of under treating severe MRSA infection in attempt to avoid relatively rare skeletal muscle toxicity not justified
      2. CPK levels should be drawn at baseline and followed once weekly there after
References:


