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High-Dose Daptomycin (>6 mg/kg) for Treatment of Severe Infections due to Staphylococci and Enterococci

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Introduction

- **Background:** Experimental and clinical studies suggest that daptomycin at high dose (>6 mg/kg) may have superior efficacy compared to normal dose (4 to 6 mg/kg), but data supporting this observation are scarce.
- **Aim:** We evaluated the efficacy and safety of daptomycin in patients receiving high-dose daptomycin (>6 mg/kg) for severe and/or complicated infections.

Methods

- **Study population:** Between 1/2009 and 4/2011, patients aged ≥18 years and diagnosed with osteomyelitis, foreign-body infection, surgical site infection or sepsis, caused by daptomycin-susceptible *Staphylococcus* spp. or *Enterococcus* spp. were included.
- **Dosing scheme:** Daptomycin was administered at >6 mg/kg every 24 h intravenously. In case of renal insufficiency (creatinine clearance <30 mL/min), the dosing interval was prolonged to 48h.
- **Efficacy assessment:** At discharge and at follow-up visits the clinical and microbiological cure was assessed. Treatment failure was classified as inadequate response to therapy (persistent infection) or relapse of infection (after an initial period of improvement).
- **Safety assessment:** Adverse events were systematically documented throughout and following the daptomycin treatment course, including anaphylaxis, rash, drug fever, nausea/vomiting, diarrhea, hepatitis, acute renal failure, eosinophilic pneumonia, rhabdomyolysis. The highest serum creatine phosphokinase (CPK) level during daptomycin therapy was documented (normal range: 25-190 U/L for men, 25-140 U/L for women). Rhabdomyolysis was defined as CPK elevation with at least one of the following symptoms: abnormal urine color, general weakness, muscle stiffness, weakness, aching or tenderness.

Results

Table 1. Demographic, clinical and infection characteristics

Characteristics	Value (n = 47)
Age (years), median (range)	68 (23-83)
Male, No. (%)	32 (68%)
Hospital stay (days), median (range)	71 (11-463)
Body Mass Index (kg/m^2), median (range)	26 (17-44)
Creatinine clearance, median (range):	75 (10-300)
>60 mL/min, No. (%)	31 (66%)
60 – 30 mL/min, No. (%)	13 (28%)
<30 mL/min, No. (%)	3 (6%)
Underlying medical conditions, No. (%):	
Diabetes mellitus	12 (26%)
Malignancy	8 (17%)
Chronic renal insufficiency (on hemodialysis)	3 (6%)
Solid organ transplants	3 (6%)
Concomitant statin therapy, No. (%)	24 (51%)
Previous antimicrobial therapy, No.	47
Vancomycin, No. (%)	29 (62%)
Other antibiotic, No. (%)	18 (38%)
Type of infection, No. (%)	
Osteomyelitis[1]	20 (43%)
Foreign-body infection[2]	19 (40%)
Surgical site infection	6 (13%)
Sepsis	2 (4%)

[1] Sternum (n=12), vertebral (n=3), other bone (n=5)
[2] Orthopedic devices (n=9), vascular prostheses (n=9), ventricular assisted device (n=1)

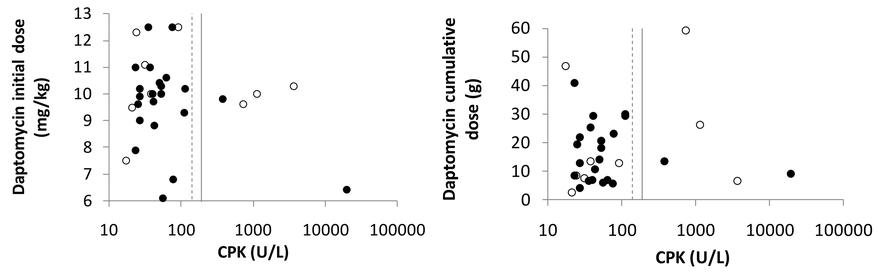
Table 2. Daptomycin therapy

Characteristics	Value
Initial dose (mg/kg), median (range)	9.8 (6.1-12.5)
Cumulative dose (g), median (range)	11.5 (2.7-59.3)
Treatment duration (days), median (range)	18 (6-89)
Reason for choosing daptomycin, No. (%):	
Expected improved efficacy	31 (66%)
Renal insufficiency	10 (21%)
Allergy to vancomycin	7 (15%)
Outpatient therapy	2 (4%)
Reduced susceptibility to glycopeptides	1 (2%)

- **Microbiology:** *Staphylococcus aureus* was isolated in 24 cases (19 MRSA, 4 MSSA and 1 VISA), *S. epidermidis* in 21 (17 MRSE) and *Enterococcus faecium* in 4 (all isolates were susceptible to vancomycin).
- **Efficacy:** Clinical and microbiological cure was observed in 41 patients (87%) with a median follow-up of 11 months; 4 patients (9%) experienced a relapse of infection and 2 patients (4%) died during hospital stay (unrelated to infection).
- **Safety:** 7 patients (15%) experienced an adverse event (**Table 3**). In 2 of 4 patients with asymptomatic CPK increase, the CPK was increased already before start of daptomycin treatment.

Table 3. Adverse event	No.
Rash	2
Rhabdomyolysis	1
Asymptomatic CPK increase	4

Figure 1. Correlation between CPK value determined in 32 patients and daptomycin initial dose (left), daptomycin cumulative dose (right). Open circles represent values for women and closed circles for men. Vertical lines represents the upper limit of CPK value for women (dashed line, 140 U/L) and for men (solid line, 190 U/L).



Conclusions

- Daptomycin at high-dose (>6 mg/kg) eradicated the staphylococcal and enterococcal infection in 87% in patients with severe and complicated infections and was well tolerated. Adverse events were observed in 7 patients (15%), in 1 patient rhabdomyolysis occurred.
- No correlation between initial or cumulative daptomycin dose and CPK increase was observed.

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