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High-dose Daptomycin Therapy for Staphylococcal Endocarditis and When to Apply It

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Abstract

Infective endocarditis (IE) continues to present a large burden to the healthcare system. *Staphylococcus aureus*, the leading pathogen associated with the disease, has always proven difficult to treat. Increasing numbers of *S. aureus* isolates are demonstrating reduced susceptibility to vancomycin, and therapeutic options are limited. Daptomycin is frequently employed when vancomycin therapy proves unsuccessful or when vancomycin MIC values rise above 1 mg/L. Currently, daptomycin is FDA-approved at a dose of 6 mg/kg/day for the treatment of *S. aureus* bacteremia and associated right-sided endocarditis. However, numerous *in vitro* and clinical studies suggest that daptomycin doses up to 12 mg/kg/day may provide improved efficacy and resistance prevention. Additionally, high-dose daptomycin has demonstrated excellent safety. Together, these data suggest a role for high-dose daptomycin in staphylococcal IE patients who are severely ill, previously failed therapy with vancomycin, or possess a *S. aureus* isolate with an elevated vancomycin MIC.

Keywords

High-dose; daptomycin; endocarditis MRSA; hVISA; VISA; *Staphylococcus aureus*; staphylococci

Introduction

Infective endocarditis (IE) represents a large burden on the healthcare system. In 2009, IE was responsible for 38,976 hospital admissions in the United States, with an estimated in-hospital mortality of 14-20%.(1, 2) *Staphylococcus aureus*, implicated in 28.7-49.3% of

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Compliance with Ethics Guidelines

Conflict of Interest

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

clinical IE cases, is the most commonly isolated IE pathogen.(1, 2) Successful treatment of *S. aureus* IE is difficult, and guidelines recommend extended antimicrobial therapy often in combination with possible surgery.(3) Even with appropriate therapy, mortality among patients with *S. aureus* IE remains high, reaching 31% in a large, multicenter trial.(4) *S. aureus* possesses many attributes that make successful treatment problematic. Compared to other bacteria, it causes increased tissue destruction, easily adheres to damaged endothelium, and often creates biofilm on both native and prosthetic surfaces.(5, 6) Compounding these issues, *S. aureus* resistance to commonly used antimicrobials is on the rise. In 2009, the rate of methicillin-resistant *S. aureus* (MRSA) implicated in IE was 53.3%, echoing the national surveillance rate of 53.5% methicillin-resistance among all *S. aureus* isolates.(1, 7) Vancomycin, the workhorse agent for MRSA endocarditis, has maintained remarkable activity against MRSA over the years. However, vancomycin therapy is not without issue. Vancomycin is slowly bactericidal, demonstrated by a median of eight to nine days for clearance of *S. aureus* bacteremia.(8, 9) Vancomycin also requires careful monitoring to ensure efficacy and avoid potential adverse effects, chief among them nephrotoxicity. Careful monitoring is of such importance that in 2009, the Infectious Diseases Society of America (IDSA), the American Society of Health-System Pharmacists, and the Society of Infectious Disease Pharmacists published guidelines regarding the dosing and monitoring of the drug, recommending a serum trough level of 15-20 mg/L in MRSA IE for a goal area under the curve (AUC)(24h)/minimum inhibitory concentration (MIC) ratio ≥400.(10) However, even with proper monitoring, IE has been implicated as an independent predictor of vancomycin treatment failure.(11) Complicating matters, in 1997, the first cases of infection due to vancomycin-intermediate *S. aureus* (VISA) and heteroresistant VISA (hVISA) were reported.(12, 13) hVISA strains are especially problematic in IE, as the high bacterial inoculum is more than large enough to house hVISA mutants, which often occur within MRSA at a rate of about one every 10^5-10^6 CFU.(14) Although hVISA can occur at vancomycin MIC values <1 mg/L, vancomycin MIC values >1mg/L are associated with hVISA, and both MIC >1 mg/L and hVISA are associated with vancomycin treatment failure.(15, 16) In studies evaluating the prevalence of hVISA within populations of patients with MRSA infections, rates of hVISA range from 2.2% to 29.2%.(17-20) From 2004 to 2009, a nationwide surveillance of *S. aureus* demonstrated an increase in the amount of isolates with vancomycin MIC ≥2 mg/L from 4% to 7.7%.(21) Due to emerging, more prevalent resistance and increasing rates of vancomycin treatment failure, therapeutic alternatives to vancomycin are necessary and warrant discussion on their proper places in therapy. Daptomycin is one such alternative, and this review intends to describe the justification and proper administration of high-dose daptomycin in the setting of IE.

Daptomycin

Daptomycin is a broad-spectrum, bactericidal, lipopeptide antibiotic derived from fermentation of *Streptomyces roseosporus*.(22) It is approved for complicated skin and soft tissue infections at a dose of 4 mg/kg once daily (cSSTIs) and *Staphylococcus aureus* bacteremia (SAB), including SAB associated with right-sided native valve endocarditis (RIE) at a dose of 6 mg/kg once daily.(23) Mechanistically, it is proposed that daptomycin achieves its antimicrobial effect by forming complexes with endogenous calcium ions, inserting its lipophilic tail into the cell membrane, and creating ion channels leading to

leakage and subsequent cell death.(24) Recently, Pogliano and colleagues further elucidated the mechanism of daptomycin with a novel experiment.(25) Their work demonstrated the ability of daptomycin to bind to and disrupt the bacterial membrane prior to cell death as well as cause the relocation of integral cellular division protein to inappropriate locations within the cell. These data suggest the dual action of daptomycin on both the cell membrane and cell wall. Daptomycin is 90-93% protein bound and is limited in its volume of distribution. It possesses a half-life of roughly eight hours and displays linear pharmacokinetics, obtaining maximum serum concentrations of 57.8 mg/L to 164.8 mg/L at doses from 4 mg/kg daily to 12 mg/kg daily.(26) Daptomycin exhibits concentration-dependent killing, and AUC_{24h} /MIC is the pharmacokinetic/pharmacodynamic parameter associated with clinical bactericidal activity.(27) Daptomycin is active against numerous Gram-positive pathogens and most importantly retains activity against MRSA with intermediate vancomycin/glycopeptide susceptibility (VISA/GISA) and vancomycin-resistant *Enterococcus* species (VRE).(24) Unlike vancomycin, which has delayed bactericidal activity, daptomycin is rapidly bactericidal against susceptible organisms *in vitro*. Clinical data suggest more rapid clearance of bacteremia with daptomycin compared to vancomycin as well, as studies demonstrate bacteremia clearance with daptomycin to be one to four days faster than with vancomycin.(28, 29) Daptomycin is less affected by the "inoculum effect" and retains bactericidal activity against bacterial counts of 10^8-10^9 CFU *in vitro*. These same bacterial burdens, often observed in IE, can render beta-lactam antibiotics and vancomycin essentially ineffective.(30, 31)

Why High-dose Daptomycin?

As mentioned, daptomycin displays concentration-dependent bactericidal activity against a variety of pathogens. Supporting the concentration-dependent activity, there are *in vitro* and *in vivo* data that demonstrate the ability of elevated doses to provide superior antimicrobial effects compared to standard dosing, especially in the setting of high inoculum infections such as IE.(32-35) Owing to the limited volume of distribution and extensive protein binding of daptomycin, it follows that higher dosing would accomplish higher concentrations at the desired infective foci as well as higher free serum drug concentrations. An inability to achieve therapeutic concentrations of drug at lower doses may contribute to treatment failure and has been shown *in vitro* to select for daptomycin nonsusceptibility.(35) Although daptomycin nonsusceptibility is still exceedingly rare clinically (<1%), high-dose daptomycin has been demonstrated *in vitro* and *in vivo* to prevent the emergence of daptomycin resistance, while standard dose therapy failed to do so.(31, 33-35) Additionally, daptomycin is frequently administered as salvage therapy after treatment failure with vancomycin. Vancomycin exposure and subsequent increases in vancomycin MIC values have been demonstrated to coincide with daptomycin nonsusceptibility.(31, 36-38) In the setting of vancomycin failure, expert opinion within the MRSA guidelines established by the IDSA recommends a daptomycin dose of 8-10 mg/kg daily, above the FDA approved dosing regimen.(39) Due to increasing clinical failures with vancomycin and daptomycin in the treatment of staphylococcal IE, along with the potential epidemiological burden of increased lipopeptide and glycopeptide resistance, numerous reports and studies have evaluated high-dose daptomycin in recent years.

In vitro and *in vivo* Studies with High-dose Daptomycin

Owing to the difficulty present in treating resistant *S. aureus* infections, numerous *in vitro* and *in vivo* studies have been undertaken in an effort to describe and understand the emergence of reduced glycopeptide and lipopeptide susceptibility in *S. aureus* isolates. Importantly, these data describe the ability of high-dose daptomycin to both prevent staphylococcal resistance and provide bactericidal activity.

Rose and colleagues evaluated clinical isolates exposed to vancomycin followed by either daptomycin 6mg/kg or 10mg/kg every 24 hours in an *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) model with simulated endocardial vegetations (SEVs) over an 8-day period.(31) Five *S. aureus* isolates, 4 methicillin-resistant and 1 methicillin-susceptible, were examined. Each of these isolates had been previously reported to develop daptomycin nonsusceptibility (DNS). Daptomycin and vancomycin MICs ranged from 0.125 to 0.25mg/L and 1-2mg/L, respectively. Similar bactericidal activity was noted for both daptomycin regimens (6 and 10 mg/kg every 24 hours) against all strains regardless of vancomycin exposure. The time to reach 99.9% kill was also similar between daptomycin regimens. Additionally, daptomycin produced the greatest reduction (average 6.1 $\log_{10}$ CFU/g) if administered prior to vancomycin exposure on day 1 versus only an average of 1.5 $\log_{10}$ CFU/g log with vancomycin administration. The MIC values for all four MRSA strains remained the same. However, one MSSA isolate developed an elevated daptomycin MIC, increasing from 0.125mg/L to 1.5 mg/L by day 7 following vancomycin exposure. This resistance occurred only in the daptomycin 6 mg/kg every 24-hour regimen, and no resistance was noted with the daptomycin 10 mg/kg every 24-hour regimen. Despite this increase in MIC, bactericidal activity was maintained throughout the experimental period.

Similarly, Steed and colleagues conducted an evaluation of high-dose daptomycin (10mg/kg every 24 hours) alone and in combination with trimethoprim-sulfamethoxazole (TMP-SMX) in an *in vitro* PK/PD model with SEVs.(40) In this 14-day evaluation, 4 DNS MRSA were evaluated. Using high-dose daptomycin plus TMP-SMX for 7 days, a substantial bactericidal reduction of >8 $\log_{10}$ CFU/g was observed, allowing for de-escalation to either daptomycin or TMP-SMX alone. Interestingly, despite daptomycin nonsusceptibility, high-dose daptomycin alone produced bactericidal activity against 3 of the 4 strains.

Chambers and colleagues evaluated simulations of standard, 6-mg/kg/day and high-dose, 12-mg/kg/day daptomycin in an *in vivo*, rabbit model of aortic valve endocarditis.(34) Two MRSA isolates were evaluated. One isolate was daptomycin susceptible (MIC 0.5 mg/L), and the other was a mutant of the first that developed daptomycin nonsusceptibility (MIC 2 mg/L) in a patient who experienced clinical failure with daptomycin and rifampin therapy. After four days, endocardial vegetations, spleens, and kidneys were harvested to evaluate daptomycin efficacy. Both dosages completely eradicated the daptomycin susceptible strain from vegetations, spleens, and kidneys. However, only the high-dose daptomycin regimen was capable of producing nearly bactericidal (2.9 $\log_{10}$ CFU/g) kill in vegetation, and the standard dose regimen reduced bacterial load by only 1 $\log_{10}$ CFU/g ($p<0.05$). Due to the extensive killing of the parent strain, the authors were unable to determine if high-dose daptomycin prevented daptomycin resistance. Together with the *in vitro* data, this study

established the necessity to evaluate clinically the use of high-dose daptomycin in the setting of high-inoculum infections such as IE.

Clinical Efficacy of High-dose Daptomycin in Infective Endocarditis

The concept of using higher doses of daptomycin has been recognized clinically since 2008.(41) In that year, there was a case report regarding the successful use of high-dose daptomycin to treat infective endocarditis and persistent bacteremia secondary to infected coronary stents.(42) The patient detailed in this report developed nosocomial infective endocarditis and was initially started on 6mg/kg/day daptomycin therapy. After nearly two weeks of persistently positive blood cultures, despite pacemaker removal, the dose of daptomycin was increased to 12 mg/kg/day, and the bacteremia cleared within 7 days. Several more case reports detailing the successful salvage of difficult-to-treat patients with high-dose daptomycin followed.(43-45) The efficacy of higher doses of daptomycin in these case reports is believed to result from the ability of higher doses to overcome the large bacterial inoculum associated with IE and more rapidly clear bacteremia. Additionally, high-dose daptomycin has been used in combination with other antimicrobials. Chen and colleagues published a case report on daptomycin nonsusceptible implantable cardiac defibrillator-related infective endocarditis that was successfully treated with 10-mg/kg/day daptomycin, intravenous fosfomycin, and concurrent surgical intervention.(46) This combination has also proven successful in three patients with methicillin-susceptible *S. aureus* (MSSA) or MRSA infective endocarditis not responding to initial therapy.(47) Avery and colleagues published a report of two cases of vertebral osteomyelitis due to DNS MRSA treated with high-dose daptomycin in combination with TMP-SMX.(48) One patient, after receipt of vancomycin therapy for 3 days, developed an MRSA isolate with vancomycin MIC 16 mg/L and daptomycin MIC 2 mg/L. This patient was treated with daptomycin 10 mg/kg/day and TMP-SMX 8 mg/kg/day (based on TMP component) for 2 months then continued on TMP-SMX oral suppression therapy for 6 months and was deemed a clinical cure at one year. The second patient received vancomycin followed by daptomycin 6 mg/kg/day with subsequent development of vancomycin and daptomycin MIC values of 4 mg/L. The patient was changed to daptomycin 10 mg/kg/day with concomitant TMP-SMX 8 mg/kg/day, and bacteremia cleared within 48 hours, although the patient died in hospital due to systemic complications. Recently, Di Carlo and colleagues reported on a case of MRSA IE with vancomycin MIC 2 mg/L.(49) After 3 days of vancomycin therapy, the patient was administered daptomycin 8 mg/kg/day in combination with TMP-SMX 15 mg/kg/day for 6 weeks followed by 6 weeks of oral TMP-SMX for suppression. Even without recommended surgical intervention, at 6-month follow-up, the patient had no documented endocardial vegetation. Beta-lactam antibiotics have demonstrated similar synergistic effects. In a recent study, Moise and colleagues evaluated daptomycin in combination with beta-lactams in cases reported to the Cubicin Outcomes Registry and Experience (CORE) database.(50) Among 33 patients with suspected *S. aureus* bacteremia secondary to an endovascular source, 9 of 10 (90%) patients treated with daptomycin plus beta-lactam achieved treatment success compared to 13 of 23 (57%) treated with daptomycin alone. Although this difference did not reach statistical significance (p=0.061), the trend warrants consideration of combination therapy and further study. Regrettably, the authors provided no data on beta-lactam selection, although they suggested the use of many agents and assumed a class effect.

In previous work, Moise and colleagues evaluated the safety and efficacy of high-dose daptomycin (≥8 mg/kg/day) recorded in the CORE database.(51) CORE, a multicenter, retrospective, observational post-marketing study started in November 2003, includes patients of all ages who received daptomycin for any duration. Data from 2005 to 2007 were reviewed and of the 3617 patients enrolled, 94 (2.6%) received daptomycin at higher doses. The most common pathogen isolated was *S. aureus* (28 isolates). The clinical success rate for MRSA was 83% among patients given high-dose daptomycin. In 2011, Kullar and colleagues assessed the clinical utility of high-dose daptomycin in a retrospective, multi-center analysis of 250 patients.(52) 218 (87.2%) patients had blood cultures positive for MRSA, 31 (12.4%) had right-sided endocarditis, and 28 (11.2%) had left-sided endocarditis. The median dose of daptomycin was 8.9 mg/kg/day, and the median duration of daptomycin therapy was 13 days. The clinical success rate, defined as resolution of signs and symptoms of infection with no further need for antibiotics or clearance of infection with negative cultures or partial resolution of symptoms with additional, step down antibiotic therapy needed, was 83.6%. 18 patients (7.2%) demonstrated clinical failure, with 11 of the 18 patients having persistently positive blood cultures. The vast majority of patients received high-dose daptomycin as salvage therapy, and the clinical success rate proved favorable for its continued utilization. Of interest, 13 patients developed daptomycin nonsusceptibility, defined as daptomycin MIC >1 mg/L(53), six of whom had endocarditis. 11 of these 13 had received prior vancomycin therapy and two had received prior standard dose daptomycin. Seven of these 13 (54%) were successfully treated with high-dose daptomycin alone or in combination with TMP-SMX or quinupristin-dalfopristin. Of the six patients with endocarditis, two were cured with high-dose daptomycin alone, and one was cured with high-dose daptomycin in combination with TMP-SMX. The success of high-dose daptomycin in this study is especially impressive given the vast majority of patients were treated with high-dose daptomycin after proving refractory to standard of care therapy. In a multicenter, prospective cohort study, Carugati and colleagues evaluated the use of high-dose daptomycin in patients with left-sided IE due to *S. aureus*, coagulase-negative staphylococci, or *Enterococcus faecalis*.(28) Among patients with left-sided IE due to *S. aureus*, 12 received high-dose daptomycin, and 74 received standard of care antibiotic therapy. 58% of *S. aureus* infections were due to MRSA. Among those infected with MRSA, high-dose daptomycin therapy significantly reduced time to clearance of bacteremia (1 vs. 5 days, $p<0.01$) and hospital length of stay (33 vs. 64.5 days, $p=0.04$). Similar to previous studies, a majority (67.9%) of patients were treated with high-dose daptomycin after initial treatment failure. Of note, no patient who was switched from vancomycin to daptomycin developed MRSA with reduced susceptibility to vancomycin. Durante-Mangoni and colleagues reported the efficacy of high-dose daptomycin in the treatment of IE in the setting of cardiac implantable electronic devices (CIED) in a series of 25 patients.(54) Treatment of these patients often proves difficult because of the biofilm commonly produced on prosthetic devices. 18 of the 25 patients required high-dose daptomycin therapy due to failure with another therapeutic regimen. Even with prior therapy, no isolate developed a daptomycin MIC value >0.5 mg/L, although 11 of 25 isolates (44%) demonstrated vancomycin MIC values of 2 mg/L. Mean daptomycin MIC_{90} values remained at 0.625 mg/L, suggesting that high-dose daptomycin may have helped curtail resistance among the isolates. The median dose of daptomycin was 8.3 mg/kg/day. Clinical success

was documented in 20 of 25 (80%) of patients, and 92% demonstrated microbiologic success. At a median follow-up of 16 months, 22 of 25 (88%) of patients were still alive, two of whom did not require CIED removal. In 2013, Murray and colleagues published a matched, retrospective cohort study comparing daptomycin to vancomycin in the treatment of *S. aureus* bacteremia with vancomycin MIC values >1 mg/L.(16) Unlike previous studies, patients in this study were ineligible for inclusion if they had received vancomycin therapy for ≥72 hours previous to daptomycin initiation. Patients received at least 6 mg/kg daily daptomycin, and the median dose was 8.4 mg/kg/day. Overall, daptomycin therapy was associated with significantly less clinical failure at 30 days compared to vancomycin (20% vs. 48.2%, $p<0.001$). Importantly, daptomycin was associated with reduced mortality at 30 days compared to vancomycin therapy as well (3.5% vs. 12.9%, $p=0.047$). In the subset of patients with IE, daptomycin therapy achieved 60% clinical success at 30 days, compared to 35% with vancomycin therapy. Patients who received daptomycin therapy were more likely to survive to hospital discharge and to still be alive at 90 days follow-up. Two patients in the daptomycin cohort developed elevated daptomycin MIC values with concomitant elevation in vancomycin MIC, one of whom was able to be treated with high-dose daptomycin alone. These data represent the largest body of evidence favoring high-dose daptomycin based solely on vancomycin MIC. In a follow-up to previous work, Kullar and colleagues published a retrospective, multicenter, observational study detailing patients with both right-sided and left-sided infective endocarditis treated with high-dose daptomycin.(55) This study is the largest to date detailing this cohort of patients. Of the 70 patients who met inclusion criteria, 54 (84.4%) were determined to have MRSA. The baseline vancomycin and daptomycin MIC_{90} values of these isolates were 2 mg/L and 1 mg/L, respectively. These patients received a median daptomycin dose of 9.8mg/kg/day, 24 patients (34.3%) were given combination therapy, and the median duration of therapy was 21 days. Clinical success was defined as in the previous study published by Kullar and colleagues. Of the 64 cases that were determined to be clinically evaluable, 55 (85.9%) were successfully treated, and survival at 30 days was 84.6%. Outcomes were similar between patients with right-sided (86.7% clinical success) and left-sided endocarditis (85.3% clinical success). Six patients had persistent bacteremia at the conclusion of high-dose daptomycin therapy, of which three were available for evaluation. One patient was cleared with daptomycin 10 mg/kg/day in combination with TMP-SMX, one was cleared with TMP-SMX alone, and the last was cleared with high-dose vancomycin after initial daptomycin therapy. MRSA with reduced susceptibility to daptomycin occurred in six patients, all of whom had received prior vancomycin therapy. Daptomycin MIC values reached 4 mg/L from starting values of 0.38-1 mg/L. Five of the six patients subsequently cleared their bacteremias, two with high-dose daptomycin alone, two with high-dose daptomycin in combination with TMP-SMX, and one with high-dose vancomycin. The data published in these studies describe the ability of *S. aureus* to develop daptomycin nonsusceptibility with standard vancomycin or daptomycin therapy while highlighting the ability of high-dose daptomycin, alone or in combination with other antimicrobials, to combat the development of such resistance. The evidence for the therapeutic efficacy of high-dose daptomycin is certainly mounting, and a list of the most important studies listed above is provided in table 1. However, concerns over adverse effects warrant consideration.

Safety of High-dose Daptomycin

Eli Lilly and Company initially discovered daptomycin in the late 1980s. However, it was abandoned due to evidence of skeletal muscle toxicity, elevations in creatine phosphokinase (CPK) and an assumed small therapeutic window.(22, 56, 57) Initially, however, this antimicrobial was tested in two divided doses, and it has since been determined that once daily dosing leads to a more favorable safety profile.(58) Concern regarding toxicity, however, remained. After its approval in 2003, Dvorchik and colleagues published a double-blind safety study of escalating doses of once daily daptomycin in healthy volunteers.(59) 24 healthy subjects were randomized to receive either daptomycin (4, 6 or 8 mg/kg/day) or control for 7 to 14 days. Elevations in CPK were seen in three patients, all were mild (350 to 477 IU/L), and one was in a control patient. Other adverse events were reported equally in both the daptomycin and control groups, including primarily gastrointestinal events. Later, Benvenuto studied doses up to 12 mg/kg/day in healthy volunteers for 14 days.(26) Again, daptomycin was generally well tolerated, and these 36 patients did not experience serious adverse events, CPK elevations, nor did they require discontinuation of therapy. In patients diagnosed with an infection, Katz and colleagues conducted a randomized study comparing vancomycin to short-course, high-dose daptomycin.(60) In a 1:1 ratio, 98 patients with cSSTI received either vancomycin 1g every 12 hours for 14 days or daptomycin 10mg/kg/day for four days. A similar amount of patients in both the vancomycin and daptomycin arms (52.1% versus 56.3%) reported adverse events. Four patients (8.3%) in the daptomycin arm experienced myopathy with concurrent elevations in CPK > 5x the upper limit of normal. Other adverse events determined to be treatment-related included nausea in 4 (8.3%) of the daptomycin patients and 2 (4.2%) of the vancomycin patients. In a retrospective chart review over a three-year period in New York Hospital, 62 patients treated with daptomycin 7 to 11 mg/kg/day for a mean of 25 days were reviewed for adverse events.(61) Although 22 of these patients experienced adverse events, only three patients experienced musculoskeletal symptoms and an increase in CPK (> 1000 IU/L). Bassetti and colleagues also performed a retrospective chart review of high-dose daptomycin.(62) 53 patients received daptomycin and 31 had doses > 6mg/kg/day with a median treatment duration of 19 days. Differences in CPK levels were not seen, and other adverse events were comparable. In 2012, Byren and colleagues conducted a randomized trial evaluating the safety and efficacy of daptomycin 6 to 8-mg/kg/day dosing in patients with prosthetic devices undergoing two-stage revision arthroplasty.(63) 74 patients were randomized to receive 6 weeks of therapy with 6 or 8-mg/kg/day daptomycin, or standard of care antibiotics. 16%, 21.7%, and 8% of patients in experienced CPK >500 U/liter in the 6-mg/kg/day, 8-mg/kg/day, and standard of care regimens, respectively, and these differences were not significant. Two patients, one from each daptomycin treatment group, experienced CPK >1000 U/liter, and both patients' CPK values returned to normal upon cessation of therapy. Withdrawal from the study due to AE was similar among all groups, although both daptomycin regimens achieved higher clinical success rates than standard of care therapy (58.3% and 60.9% vs. 38.1% for 6 and 8-mg/kg/day vs. standard of care, respectively). High-dose daptomycin was also studied with concomitant statin therapy.(64) This retrospective study evaluated 100 patients receiving high-dose daptomycin, 36 of which received concomitant statins. CPK elevations were equally distributed between patients receiving statin therapy and those not receiving statin therapy, and there were no instances

of clinical muscle toxicity. Carugati and colleagues reported adverse effects related to daptomycin therapy in 3 (10.7%) patients.(28) One patient developed CPK elevation, and 2 developed nervous system disorders. Upon analysis of their data, daptomycin ≥8 mg/kg/day was not significantly associated with adverse events compared to daptomycin <8 mg/kg/day. Durante-Mangoni and colleagues reported CPK elevations <3x ULN in 5 patients (20%).(54) 4 of the 5 patients continued daptomycin therapy with subsequent reduction of CPK levels, and the fifth was taken off of therapy due to assumed therapeutic failure. In the first study by Kullar and colleagues evaluating high-dose daptomycin, 8.5% of patients had CPK levels >200 U/L, and the maximum value was 604 U/L.(52) No correlation was demonstrated between daptomycin dose and elevated CPK level (r=0.042, p=0.63), all patients with CPK elevation were asymptomatic, and CPK elevations were reversible upon cessation of daptomycin therapy. The authors' subsequent study provided similar results, with only 2 (2.9%) patients on daptomycin therapy experiencing treatment-related adverse effects.(65) Interestingly, neither patient had notable elevations in CPK, as one patient developed hyperkalemia and the other thrombocytopenia. The thrombocytopenic patient remained on high-dose daptomycin therapy, and platelet count recovered. In a recent study by Casapao and colleagues, high-dose daptomycin was shown to be efficacious and tolerable in the setting of enterococcal infection.(66) No patients experienced adverse effects attributable to high-dose daptomycin. Similar to previously published data, no correlation was found between daptomycin dose and CPK elevation (r=0.07, p=0.28). In a retrospective analysis of a subset of patients from the pivotal, phase III trial comparing daptomycin to standard of care in *S. aureus* bacteremia, Bhavnani and colleagues used population pharmacokinetic modeling to estimate the relationship between daptomycin dose and elevated CPK.(9, 67) 108 patients who received daptomycin 6 mg/kg/day for at least 10 days were included, of whom 6 (5.56%) developed CPK elevation. Of these 6 patients, 3 (50%) had a daptomycin minimum serum concentration >24.3 μg/ml, leading to the observation that CPK elevation is associated with minimum concentrations ≥24.3 μg/ml. Of note, only 2 of these 6 patients developed musculoskeletal adverse events, and 4 of the 6 were >111 kg and received substantially larger than normal doses. Given that these patients received 6 mg/kg/day, it would seem logical that daptomycin serum minimum (trough) concentrations ≥24.3 μg/ml occur frequently with higher dosing. However, the data with high-dose daptomycin thus far have not registered higher rates of elevated CPK concentrations or toxicity. Overall, the data on the safety of high-dose daptomycin are encouraging. CPK elevation, the most commonly reported adverse event attributable to daptomycin therapy, is a sensitive marker of inflammation and as such is often transient and secondary to other comorbidities the patient may be experiencing. Serum CPK levels should be monitored weekly while on daptomycin therapy, but they are a marker and do not alone confer an adverse effect. Careful monitoring of patient CPK and musculoskeletal complaints is paramount to allow for confident use of high-dose daptomycin therapy.

Conclusions

Staphylococcal IE is a difficult disease requiring complicated therapeutic decision-making. Modern medical and surgical therapies have decreased mortality, but bacterial resistance is an ever-present and evolving problem requiring creative therapeutic solutions. Recent data

illustrate the efficacy of high-dose daptomycin in the treatment of staphylococcal IE. Because of its concentration-dependent activity, high-dose daptomycin has the ability to overcome a large bacterial inoculum, penetrate bacterial biofilm, and prevent the emergence of bacterial resistance. Given the large bacterial burden, biofilm formation, and emerging resistance to glycopeptides present in IE, high-dose daptomycin should be considered a regimen of choice. In patients with persistent bacteremia on vancomycin therapy, high-dose daptomycin should be strongly considered. Similarly, given the strong correlation between elevated vancomycin MIC (>1) and treatment failure, high-dose daptomycin therapy should be considered as first line therapy if such a strain is present. High-dose daptomycin has demonstrated efficacy in the presence of CIED infections, and as such should be considered as an early therapeutic option. Because daptomycin is rapidly bactericidal compared to vancomycin and more expeditiously clears bacteremia, high-dose daptomycin should be considered in septic patients given the importance of rapid clearance of infection. The addition of other antimicrobial agents is intriguing and should certainly be considered in all infections involving necessitation of high-dose daptomycin. Numerous case series and reports have demonstrated the efficacy of such combinations, and combining daptomycin with a beta-lactam, TMP-SMX, or other agents may provide better activity and further prevent resistance compared to daptomycin monotherapy. Overall, high-dose daptomycin demonstrates clinical efficacy and remarkable tolerability and should be considered a viable treatment option, especially in areas with endemic *S. aureus* glycopeptide resistance.

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Michael J. Rybak is the guarantor of this article and takes responsibility for the integrity of the work as a whole.

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Table 1

Selected studies evaluating the safety and utility of high-dose daptomycin

Authors	Type of Study	Patient Population	Number of Patients	Daptomycin Therapy	Results and Major Conclusions	Reference
Moise PA, et al. 2009	Retrospective, observational	Subset of patients 18 years or older from the Cubicin Outcomes Registry and Experience (CORE) database with any site of infection	Total = 94 IE = 15	Median daily dose of 8 mg/kg for 15 days (1 – 90 days)	Clinically evaluable subset of 74 patients. Clinical cure or improvement in 89% of all patients. Clinical cure or improvement in IE of 69%. Two patients discontinued daptomycin secondary to adverse events	51
Kullar R, et al. 2011	Retrospective, observational	Patients 18 years or older with confirmed or suspected Gram-positive infections (S. aureus or enterococci) at any site	Total = 250 IE = 31	Median daily dose of daptomycin was 8.9 mg/kg (IQR 8.0 – 10.0 mg/kg) for 10 – 13 days (IQR 5 – 18 days) depending on organism	Clinically evaluable subset of 227 patients. Clinical cure or improvement in 83.6%. Clinical failure in 5 IE patients	52
Carugati, et al. 2013	Prospective, cohort	Subset of patients 16 years or older from the International Collaboration on Endocarditis Daptomycin Study (ICE-DS) database with left-sided endocarditis	Total (IE) = 178 Daptomycin treated = 29	Median daily dose of 9.2 mg/kg (range, 7.7 to 10.0 mg/kg) for 39 days (range, 25.0 to 43.0 days)	Time to clearance of bacteremia was significantly faster with daptomycin (1 versus 5 days). Higher dose daptomycin was not associated with an increase in adverse events	28
Durante-Mangoni, et al. 2012	Case series	Patients with staphylococcal infective endocarditis on a cardiac implantable electronic device	Total = 25	Median daily dose of 8.3 mg/kg (6.4 – 10.7) for 20 days (8 – 52)	All patients were clinically evaluable. Clinical success of 80%. No serious adverse events related to high-dose daptomycin	54

Authors	Type of Study	Patient Population	Number of Patients	Daptomycin Therapy	Results and Major Conclusions	Reference
Murray KP, et al. 2013	Matched retrospective, cohort	Patients with MRSA bacteremia on vancomycin or daptomycin matched according to age, Pitt bacteremia score, and source of bacteremia	Total = 170 Daptomycin IE = 20	Median daily dose of 8.4 mg/kg (IQR 6.3 – 9.9 mg/kg)	Clinical failure at 30 days was significantly lower in the daptomycin-treated patients. Daptomycin treatment was associated with reduced mortality compared to vancomycin (3.5% vs. 12.9%, p=0.047).	16
Kullar R, et al. 2013	Retrospective, observational	Patients with definitive or possible RS and/or LS IE	Total = 70 RS IE = 33 LS IE = 35 LS/RS = 2	Median daily dose of daptomycin was 9.8 mg/kg (IQR 8.2 – 10.0 mg/kg) for	Clinically evaluable subset of 64 patients. Clinical success in 85.9% of patients. Two patients experienced adverse events secondary to daptomycin	55

*IE = infective endocarditis, IRQ = Interquartile range, RS = right-sided, LS = left-sided