Healthy Aging & Clinical Care in the Elderly

REVIEW

Daptomycin for Treatment of Complicated Skin and Skin Structure Infections

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Abstract: Acute bacterial skin and skin structure infections (ABSSSI) are common in the elderly and are often complicated due to several factors, including higher prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) and presence of comorbidities compared to younger patients. Daptomycin, a cyclic lipopeptide, exhibits excellent *in vitro* bactericidal activity against MRSA and other Gram-positive bacteria associated with complicated skin and skin structure infections (cSSSI). Daptomycin achieves adequate drug penetration into inflamed soft tissues, and is primarily cleared by the kidneys. Typical daptomycin dosing for cSSSI is 4 mg/kg, using actual body weight. While some data are available for the safety and efficacy of doses up 12 mg/kg, higher doses should be reserved for serious and invasive infections.

In comparative studies daptomycin was non-inferior to comparator drugs (including vancomycin or penicillinase-resistant penicillins) for treatment of cSSSI. The overall response rate for daptomycin was greater than 80%. Post-marketing analyses of daptomycin therapy for cSSSI have shown similar clinical success of greater than 80%, even in older patients.

Daptomycin was generally well-tolerated. The most common side effects were constipation, nausea, and headaches. The incidences of muscle toxicity were similar between daptomycin and comparator antibiotics (less than 5%). However, the risk of skeletal muscle toxicity may increase when higher doses of daptomycin are used. As such, creatinine phosphokinase should be monitored regularly while a patient is on daptomycin therapy. If possible, daptomycin susceptibility should be performed at baseline and when treatment failure is suspected.

Based on the current available data, daptomycin appears to be a viable alternative to standard treatment options for cSSSI.

Keywords: daptomycin, skin and skin structure infection, cellulitis, soft tissue infection, MRSA, pharmacology

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Introduction

Acute bacterial skin and skin structure infections (ABSSSI), also known as skin and soft tissue infections, vary widely in presentation and severity. The two main categories are complicated skin and skin structure infections (cSSSI) and uncomplicated skin and skin structure infections (uSSSI).[1] Characterized by extensive or deep tissue involvement, patients who present with cSSSI usually exhibit systemic signs infection, such as leukocytosis and fever, that are typically absent in uSSSI. Examples of cSSSI include major abscesses, infected ulcers, and surgical site infections. Patients with cSSSI often require initial hospitalization for treatment with intravenous (IV) antibiotics and if necessary, infection site management, such as incision and drainage.[2–5] In contrast, uSSSI can often be successfully treated with oral antibiotics or local care in the outpatient settings.[3,4]

The elderly are at high risk for ABSSSI for several reasons. Older patients have natural decline in immune function, increasing fragility of the skin due to atrophy and reduced cell turnover, as well as presence of chronic comorbidities such as diabetes that predispose them to infection.[6–9] A national survey of approximately 85 million physician office visits for skin and skin structure infections from 1993 to 2005 showed increased number of office visits by older patients than younger patients.[10] In fact, patients 50 to 59 years old had 24 visits per every 1000 US population years (USPY), 60 to 69 year olds had 28 visits per 1000 USPY, 70 to 79 year olds had 32 visits per 1000 USPY, and those 80 years or greater had 46 visits per 1000 USPY. A study of infections in 113 Veterans Affairs Community Living Centers (ie, nursing homes), where 83.4% of 10,939 patients were over 60 years old, showed that ABSSSI (including cellulitis, soft tissue, and decubitous ulcers) accounted for 23.9% of 619 infections reported trailing behind only urinary tract infections.[11]

Older patients are also at increased risk for complications from cSSSI, as aforementioned comorbidities, like diabetes, predispose them to treatment failure and significant morbidity and mortality.[7,8] The elderly also have increased likelihood of being infected with resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), which are often associated with poor outcomes.[12,13] In one analysis of 4,334 patients with *S. aureus* infections in Asia, elderly patients (65 years or older) had significantly higher rates of MRSA (53% in older vs. 35% in younger, $P < 0.05$) and higher 30-day mortality (overall: 22.7% in older vs. 8.7% younger patients; ABSSSI-specific: 6.5% in older vs. 1.6% in younger patients; both $P = <0.001$).[12]

Staphylococcus aureus and β-hemolytic streptococci are the leading pathogens that cause cSSSI, although enterococci and Gram-negative bacteria may also cause infections in patients with chronic ulcers, such as diabetics.[4,8,14,15] In the past decade, ABSSSI caused by MRSA has increased dramatically.[3,14,15] A surveillance study estimated that the rate of ABSSSI caused by MRSA in North America augmented from 26% in 1998 to 47% in 2004.[14] Another surveillance study estimated that 59% of 619 patients who presented to 12 emergency departments within the United States had ABSSSI caused by MRSA.[15]

The increase in MRSA rates for ABSSSI is likely driven by the rise of community-associated MRSA (CA-MRSA), since the incidence of infections caused by healthcare-associated MRSA (HA-MRSA) seems to be declining.[16] Both CA-MRSA and HA-MRSA contain *mecA*, the gene that renders *S. aureus* resistant to beta-lactams. However, they are thought to be genetically distinct, as CA-MRSA contains the unique staphylococcal cassette chromosome mec (SCC*mec*) type IV and some produce the Panton-Valentine leukocidin (PVL) cytotoxin not found in HA-MRSA.[17]

These and other differences support some of the unique epidemiologic and phenotypic characteristics of CA-MRSA. Unlike HA-MRSA, CA-MRSA can cause infections in individuals without typical risk factors for resistant organisms. Most people infected with CA-MRSA presents with ABSSSI, but it can also cause more severe infections like necrotizing pneumonia and endocarditis. There is also evidence of increasing incidence of healthcare-associated infections being caused by CA-MRSA as well.[18,19]

Community associated-MRSA isolates are generally susceptible to many non-beta lactam antibiotics such as trimethoprim-sulfamethoxazole, doxycycline, and clindamycin, unlike HA-MRSA which are typically resistant to many different antibiotic classes.[17] Vancomycin and newer MRSA-active antibiotics, such as daptomycin and linezolid, have excellent activity against both CA-MRSA and HA-MRSA.[3,17]

The increasing prevalence of MRSA as a cause of ABSSSI has made vancomycin become the empiric IV

antibiotic of choice for many clinicians to treat patients presenting with ABSSSI in the hospital setting.[3,20] However, the utility of vancomycin has been called into question based on consistent evidence demonstrating its reduced effectiveness in treating serious infections caused by MRSA with upper limit of vancomycin susceptibility (minimum inhibitory concentration [MIC] of 2 mcg/mL).[20–23] The joint consensus guidelines on vancomycin therapy by the American Society of Health-Systems Pharmacists (ASHP), Infectious Diseases Society of America (IDSA), and Society of Infectious Diseases Pharmacists (SIDP) suggest the use of alternative agents active against MRSA when the MIC is 2 mcg/mL or more.[20]

Daptomycin (Cubicin® marketed by Cubist Pharmaceuticals) is one such alternative agent, along with other newer antibiotics, linezolid, ceftaroline, quinupristin-dalfoprisin, and tigecyline.[3] Daptomycin is a cyclic lipopeptide antibiotic with activity against many gram positive bacteria, including multi-drug resistant organisms.[24–27] Approved in 2003, daptomycin is FDA indicated for treatment of cSSSI, bacteremia, and uncomplicated right-sided infective endocarditis caused by susceptible gram positive bacteria in adults.[28] This review will focus of the current evidence for use of daptomycin in the treatment of cSSSI.

Clinical Pharmacology

Mechanism of action and pharmacodynamics

Daptomycin exhibits rapid, concentration-dependent, bactericidal activity through calcium-dependent binding to the plasma membrane to elicit membrane potential depolarization. This loss of potential causes inhibition of DNA, RNA, and protein synthesis to result in cell death.[29] Apparent for its concentration-dependent pharmacodynamic property, in vitro studies have demonstrated that higher daptomycin doses of 10 mg/kg display more rapid killing rate compared to smaller doses of 6 mg/kg.[30,31] The ratio of total exposure, represented by area under the curve (AUC), to MIC (AUC:MIC) is the best pharmacodynamic index predictive of daptomycin clinical activity.[32]

Spectrum of activity

Daptomycin exhibits activity against most pathogenic Gram-positive bacteria, including *S. aureus* (both MRSA and methicillin sensitive *S. aureus* [MSSA]), β-hemolytic streptococci, and enterococci (including vancomycin resistant enterococcus [VRE]). Daptomycin is not active against Gram-negative bacteria.[24–27] Determined by Clinical Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the MIC breakpoints of daptomycin for susceptible isolates of *S. aureus* and β-hemolytic streptococci are both ≤1 mcg/mL, and ≤4 mcg/mL for susceptible enterococci.[28,32] Any isolates with MICs above these breakpoints are considered "non-susceptible" as no concrete MIC ranges for intermediate and resistant strains have been established. In vitro susceptibilities of clinical Gram-positive isolates collected from North American and European hospitals between 2002 and 2006 have been evaluated in four studies.[24–27] Greater than 99% of the 33,000 plus isolates collected from these studies (including MRSA, MSSA, β-hemolytic streptococci, and enterococci) were susceptible to daptomycin (Table 2).

Pharmacokinetics

The pharmacokinetic (PK) parameters of daptomycin are summarized in Table 3. Daptomycin serum peak concentrations (Cmax) are reached within 30–60 minutes after the end of a 30-minute IV infusion. Within the typical therapeutic dosing ranges and interval, the steady-state Cmax and AUC of daptomycin rises proportionally to increasing doses, indicating a linear pharmacokinetic relationship. Daptomycin exhibits a relatively small volume of distribution (Vd) of 0.1 L/kg, and is highly bound to serum albumin (~91%), albeit reversibly.[33,34]

Daptomycin's ability to penetrate inflamed soft tissue was assessed in a study that evaluated blister fluid concentrations in seven healthy volunteers.[35] Twenty-four hours after a single 4 mg/kg dose, daptomycin exposure in the blister fluid was 68% of the serum concentration. Mean blister fluid daptomycin Cmax was 27.6 mcg/mL that took 3.7 hours to reach maximum value, compared to serum Cmax at 77.8 mcg/mL after 30 minutes.

Daptomycin does not appear to induce, inhibit, nor serve as a substrate for any major CYP450 enzymes.[28] Daptomycin is primarily cleared via renal elimination, with ~50% of dose being recovered in the urine after 24 hours.[33] The mean half-life ($t_{1/2}$) of daptomycin in healthy volunteers with normal renal function was

Table 1. Commonly used abbreviations.

ABSSSI	Acute bacterial skin and skin structure infections
AUC	Area under the curve
CA-MRSA	Community associated methicillin resistant *Staphylococcus aureus*
Cmax	Peak concentration
CORE	Cubicin Outcomes Research and Experience
CPK	Creatinine phosphokinase
cSSSI	Complicated skin and skin structure infections
GFR	Glomerular filtration rate
HA-MRSA	Healthcare associated methicillin resistant *Staphylococcus aureus*
HD	Hemodialysis
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme-A
hVISA	Vancomycin heteroresistant *Staphylococcus aureus*
IBW	Ideal body weight
INR	International normalized ratio
IV	Intravenous
MIC	Minimum inhibitory concentration
MRSA	Methicillin resistant *Staphylococcus aureus*
MSSA	Methicillin sensitive *Staphylococcus aureus*
PK	Pharmacokinetics
PRP	Penicillinase-resistant penicillin
TBW	Total body weight
ULN	Upper limit of normal
USPY	United States population years
uSSSI	Uncomplicated skin and skin structure infections
Vd	Volume of distribution

approximately 8 hours and steady-state concentrations were achieved after 3 days of therapy.[33,34] In patients with severe renal function (creatinine clearance [Clcr] < 30 mL/min), the $t_{1/2}$ was prolonged 3–4 times that of patients with normal renal function.[28]

In a single-dose study, the PK of daptomycin in healthy elderly patients (>75 years old) were compared to that of young adults (18–30 years old).[36] There was no significant difference in serum Cmax or Vd; however, the mean AUC was higher by 58% and mean clearance was lower by 38% in elderly subjects compared to that of young subjects. These differences are primarily contributed by the age-related decrease in renal function that is expected with advancing age. Despite these results, no empiric dose adjustments for age are recommended for geriatric patients based solely on age.

The effects of obesity on daptomycin PK have been evaluated in two single dose studies using 4 mg/kg of daptomycin.[37,38] Both studies found that Cmax and AUC were significantly higher (by 25%–60% and 30%–61%, respectively) in the obese groups compared to non-obese patients. However, when normalized to total body weight (TBW), this significance disappeared.[38] Total Vd was also higher in the obese groups. When normalized to TBW, Vd was significantly lower in the obese group (0.09–0.11 L/kg in obese vs. 011–0.13 L/kg in non-obese).[37,38] Based on the safety and the potential under-exposure using IBW, the investigators from both studies recommended using TBW for dosing daptomycin.

One of the studies also compared glomerular filtration rate (GFR) estimation in morbidly obese patients using TBW and IBW with the Cockcroft-Gault (CG) and the four-variable modification of diet in renal disease (MDRD) equations.[38] Using IBW in either equations closely approximated the true GFR in both obese and non-obese groups, while TBW overestimated clearance by more than 200% in morbidly obese patients. Thus, the investigators recommended calculating GFR using IBW.

Table 2. Combined results from four studies that tested in vitro activity of daptomycin on clinical gram positive Isolates from North American and European hospitals from 2002–2006.[24–27]

Organism (# of isolates)	MIC range	% susceptable
North America		
S. aureus		
MRSA (11548)	≤0.06 to 2	>99.9
MSSA (11245)	≤0.06 to 2	>99.9
β hemolytic streptococci* (2321)	≤0.06 to 0.5	100
Enterococci		
E. faecalis+ (5480)	≤0.06 to 8	>99.9
E. faecium^ (2903)	≤0.06 to 8	>99.9

Notes: *All isolates were 100% vancomycin and penicillin sensitive; +99% ampicillin sensitive, 96% vancomycin sensitive; ^7% ampicillin sensitive, 38% vancomycin sensitive (more common in European isolates).

Drug Interactions

While there is no known pharmacokinetic interaction with 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitors (ie, statins), both daptomycin and HMG-CoA reductase inhibitors may independently increase the risk for skeletal muscle toxicity that may manifest as creatinine phosphokinase (CPK) elevation and myopathy.[2,28] Therefore, if

possible, HMG-CoA reductase inhibitors should be temporarily discontinued for the entire duration of daptomycin therapy.

Daptomycin may cause a concentration-dependent false elevation of the international normalized ratio (INR) with prolongation of prothrombin time (PT) resulting from interactions with some test reagents.[28] For patients who take warfarin while on daptomycin therapy, patient's anticoagulation status should be closely monitored. If an interaction is suspected, blood sampling for INR testing should be conducted immediately before the next administration of daptomycin when drug concentrations are at their lowest. Alternatively, another reagent to test the INR should be used.

Resistance

Daptomycin non-susceptibility have been both induced in vitro and isolated during daptomycin treatment. However, daptomycin non-susceptiblity remains rare.[39–46] Mechanisms of daptomycin resistance are not fully elucidated, but gene mutations that alter membrane potential and permeability have been identified in *S. aureus* and enterococci.[39–41]

Reduced susceptibility to daptomycin among vancomycin-intermediate *S. aureus* (VISA) and vancomycin-heteroresistant *S. aureus* (hVISA) has been documented in literature.[47–49] The thicker cell wall seen in VISA and hVISA, as compared to other *S. aureus* strains, is hypothesized to impede diffusion of daptomycin to the binding sites on the bacterial membrane and thereby promotes resistance.[45–49] Isolates of MRSA with MIC of 2 mcg/mL may harbor hVISA sub-populations[48,50] There has been concern that daptomycin may therapeutically fail against infections caused by MRSA with high MICs, if treated with vancomycin first, since sub-therapeutic troughs of vancomycin may select for hVISA sub-populations.[20] However, the clinical implication of the presence of hVISA sub-populations is not clear. In a retrospective analysis of patients treated with daptomycin, there were no significant differences in treatment outcomes when stratified into *S. aureus* with vancomycin MIC ≥ 2 or <2 mcg/mL.[51] Of note, 58% of 442 patients who received antibiotics prior to daptomycin therapy were initially treated with vancomycin and there were no significant differences in vancomycin use between the two groups. Furthermore, in two large in vitro susceptibility studies evaluating isolates of MRSA with vancomycin MIC of 2, daptomycin remained highly active with susceptibility ranging from 97% to100%.[50,52]

In situations where daptomycin resistance developed during treatment, most patients had severe infections with high bacterial inocula (eg, osteomyelitis, prosthetic associated infections, and endocarditis); often lacked or had delay in proper surgical interventions; and had presumed sub-optimal drug concentration to target tissues as evident by prolonged bacteremia.[42–46] To reduce the probability of developing resistance and treatment failure, surgical intervention to remove the source of infection should be performed, if possible.[3,5,8] If patients are initiated on vancomycin therapy empirically, vancomycin therapy should be optimized in accordance with the ASHP's vancomycin guidelines to reduce the risk of selection for hVISA sub-strains.[20]

Efficacy

Comparative studies

Results from daptomycin comparative studies for treatment of cSSSI are summarized in Table 4.

Table 3. Daptomycin pharmacokinetic parameters.[28,33,34]

Pharmacokinetic parameter	Value
$Cmax_{serum}$ at steady-state	
4 mg/kg/day after day 7	57.8 mcg/mL
6 mg/kg/day after day 4	93.9 mcg/mL
8 mg/kg/day after day 4	123.3 mcg/mL
10 mg/kg/day after day 4	141.1 mcg/mL
12 mg/kg/day after day 4	183.7 mcg/mL
Half-life	
Clcr^ $>$ 80 mL/min	9.4 hours
Clcr^ 50–80 mL/min	10.8 hours
Clcr^ 30–50 mL/min	14.7 hours
Clcr^ $<$ 30 mL/min	28 hours
Hemodialysis	30.5 hours
CAPD	27.6 hours
Volume of distribution	~0.1 L/kg
Protein binding	91%, reversible
AUC_{0-24h} at steady-state	
4 mg/kg/day after day 7	494 mcg*h/mL
6 mg/kg/day after day 4	632 mcg*h/mL
8 mg/kg/day after day 4	858 mcg*h/mL
10 mg/kg/day after day 4	1039 mcg*h/mL
12 mg/kg/day after day 4	1277 mcg*h/mL

Note: ^Clcr = Creatinine clearance calculated using Cockcroft-Gault equation.

Daptomycin was approved by the US Food and Drug Administration for cSSSI based on two prospective, randomized, non-inferiority, phase III clinical trials.[2] Patients presenting with cSSSI were randomly assigned to receive daptomycin or conventional therapy using either vancomycin, or penicillinase-resistant penicillin (PRP—cloxacillin, nafcillin, oxacillin, or flucloxacillin). The addition of aztreonam and metronidazole were permitted when clinically warranted. Patients received at least 96 hours of their initial therapy. If there was significant clinical improvement and there were compelling reasons to do so (eg, need to leave hospital, loss of IV access), patients were allowed to be switched to oral therapy (drugs not specified in study) to finish a 7- to 14-day course. However, 90% of patients in both groups remained on their initial treatment for the duration of their therapies.

In the analysis of 913 clinically evaluable subjects with 429 in the daptomycin and 484 in the conventional therapy groups (ie, 299 received PRP and 185 received vancomycin), there were no significant differences in the clinical success between the groups (83% with daptomycin vs. 84% with conventional therapy).[2] In addition, significant differences in the treatment outcomes were not detected in any of the subgroup analyses. While there were no statistical differences between the treatment arms, patients presenting with confirmed MRSA infections had overall lower clinical success compared to those with MSSA infections (86% in MSSA daptomycin group and 87% in MSSA standard therapy group vs. 75% MRSA daptomycin group and 69% MRSA standard therapy group). The investigators reported that this disparity was likely due to the higher prevalence of comorbidities in patients with MRSA than those with MSSA infections.[13] This was corroborated in a sub-analysis of diabetic patients. Diabetic patients were older than the overall study population by approximately 10 years (60 to 63 years old in diabetic patients vs. 52 years old in the study population). In addition, diabetic patients achieved lower clinical success as compared to the rest of the study population (66% and 70% in diabetic daptomycin and comparator subsets vs. 83% and 84% in overall daptomycin and comparator groups).[2,7]

In an open-label, prospective study of hospitalized patients with cSSSI, daptomycin was compared to vancomycin that was historically matched on a 1 to 4 ratio.[53] The speed of clinical improvement, clinical outcomes, and economic impact were assessed. Patients were required to receive at least 3 days of daptomycin or vancomycin for up to 14 days. Aztreonam, tobramycin, or metronidazole were added by treatment team if determined necessary. Overall, 100% patients in both groups had clinical resolution of their infection by the end of the 14-day study period. However, a higher proportion of daptomycin group had clinical success on both days 3 and 5 (90% vs. 70% and 98% vs. 81%, respectively, both $P < 0.01$). In addition, the speed of clinical improvement was significantly faster by 3 days in the daptomycin group as compared to the vancomycin group. The median duration of IV therapy was 4 days for the daptomycin group vs. 7 days for the standard treatment ($P < 0.01$). Notably, these results may have been confounded by a significantly higher number of patients with confirmed MRSA in the vancomycin group as compared to the daptomycin group (75% vs. 42%, $P < 0.001$). Compared to daptomycin, significantly more patients in the vancomycin group also had prior antibiotic exposure and previous hospitalizations.

Based on the observation that patients receiving daptomycin appeared to exhibit rapid clinical improvement, a pilot study was conducted to evaluate the efficacy and safety of high-dose, short-duration daptomycin therapy for treating cSSSI.[54] Patients received either daptomycin 10 mg/kg once daily for 4 days only, vs. standard therapy (ie, vancomycin or PRP) for 4 to 14 days. Patients in either groups were allowed to switch to oral antibiotics after 4 days of therapy if significant clinical improvement was noted. No significant difference in clinical success between the two groups was observed, although fewer patients on daptomycin, as compared to standard therapy, responded to treatment (82% vs. 95%, respectively). For confirmed MRSA infections, significantly fewer patients in the daptomycin group achieved clinical success as compared to standard treatment (Table 4). As this study was likely underpowered, larger studies are needed in order to assess the utility of high-dose, short-term daptomycin therapy.

A recent meta-analysis analyzed the aforementioned three comparative trials, along with one comparative daptomycin trial for uSSSI. No significant differences in outcomes were found between daptomycin and standard treatments.[55] In summary of clinical trials for the treatment of cSSSI, daptomycin appears to be as efficacious as the comparator standard treatment, namely vancomycin and PRP. Whether patients on daptomycin treatment truly exhibit faster clinical improvement compared to those who receive standard treatment is unclear, as the current available data is conflicting.

Postmarketing analyses

There have been several postmarketing surveillance analyses of daptomycin treatment. Most of data were derived from the Cubicin Outcomes Research and Experience (CORE) program, which is a multi-centered clinical database of patients who received daptomycin treatment in the United States.[56–59] Similarly, the European Cubicin Outcomes Research and Experience (EU-CORE) maintains data of patients who received daptomycin in Europe.[60] The rates of clinical successes from these post-marketing analyses of daptomycin for treating cSSSI were comparable to that of the clinical trials, with efficacy greater than 80% (Table 5).[56–60] This held true in various sub-analysis of CORE data of patients with MSSA and MRSA infections.

Safety

Daptomycin therapy is generally well tolerated. In two cSSSI phase III trials, discontinuation rates for in patients receiving daptomycin treatment were low and similar to standard therapy (2.8% in both groups).[2] The most common side effects reported were constipation, nausea, and headaches. Elevation of CPK enzymes associated with the use of daptomycin was low at 2.1% vs. 1.4% with standard treatment (P = NS). Only two patients were discontinued from daptomycin resulting from CPK elevation and one experienced symptoms of muscle toxicity.

Skeletal muscle toxicity has long been a concern of daptomycin therapy. In fact, early clinical trials with daptomycin administered twice a day was associated with CPK and myopathies.[61] Later studies reported that once daily dosing minimized this toxicity, suggesting that daptomycin associated muscle toxicity may be related to elevated trough concentrations.[33,34,61] Despite the reduction in risk by prolonging the dosing interval, increasing the dose of daptomycin may place patients at high risk for CPK elevation. In a phase III clinical trial evaluating daptomycin 6 mg/kg/day for treatment of endocarditis and bacteremia, significantly more patients in the daptomycin group experienced CPK elevation of >500 IU/L compared to standard treatment (9.5% of 116 vs. 1.5% of 111, P = 0.04). However, only three of these patients required discontinuation of daptomycin.[62]

A retrospective analysis of 61 patients who received high-dose, long term daptomycin therapy in one hospital demonstrated that daptomycin was well-tolerated.[63] The median daily dose and duration of therapy were 8 mg/kg and 25 days (range 14–82), respectively. Three patients experienced symptoms of muscle toxicity along with CPK > 10 times upper limit of normal (ULN) that subsequently required discontinuation of therapy.

Postmarketing surveillance has shown similar findings as the clinical trials. Analyses from CORE data demonstrated that adverse drug events associated with daptomycin therapy were low (6%–7%) and mostly mild in severity. Both discontinuations from therapy and CPK elevations with or without myopathy were infrequently reported at <5%.[56–58] Most patients who were identified with CPK elevations in postmarketing analysis were generally receiving higher doses of daptomycin (6–10 mg/kg), or initially received unadjusted doses despite severe renal dysfunction.

Other severe adverse effects associated with daptomycin therapy have been recorded in clinical trials and postmarketing surveillance. These reactions consist of eosinophilic pneumonia, rhabdomyolysis, and peripheral neuropathy.[28,62,64–66] However, these effects remain rare.

Dosage and Administration

The manufacturer recommends 4 mg/kg IV every 24 hours of daptomycin for treating cSSSI.[28] For cSSSI associated with bacteremia or involving the bone or joint, doses >4 mg/kg may be warranted. While the optimal dose for cSSSI has not been established, there is some data on the safety and efficacy of doses up to 12 mg/kg[57,63] However, clinical

Table 4. Comparative studies of daptomycin for complicated skin and skin structure infections.

Study	Design	Age range	Treatment	CE		
				D	C	*P*
Arbeit et al[2]	Multi-centered RCTs	18–85 years old	D 4 mg/kg/day for 7–14 days or ST# for 7–14 days	372/446 (83%)	384/456 (84%)	NS
Davis et al[53]	Open labeled, historical control	18–85 years old	D 4 mg/kg/day for 3–14 days or V 1 g BID for 7–14 days^	53/53 (100%)	212/212 (100%)	NS
Katz et al[54]	Multi-centered, pilot RCT	>18 years old	D 10 mg/kg/day for 4 days or ST# for 10–14 days	32/39 (82%)	37/39 (95%)	NS

information for doses exceeding 6 mg/kg are limited and these high doses are generally used for other serious types of infections such as osteomyelitis or meningitis.[57,67] Actual body weight should be used to determine the patient-specific dose.[37] However, caution should be applied when using high doses in obese patients as they may achieve higher exposure from reduced Vd when compared to non-obese patients.[37,38]

The frequency of dosing daptomycin is determined by renal function. While creatinine clearance was calculated using TBW in clinical trials, the potential for overestimation of renal function, especially in obese patients, makes the use of IBW more appealing.[38] For patients with severe renal dysfunction (creatinine clearance <30 mL/min), undergoing hemodialysis (HD), or continuous ambulatory peritoneal dialysis (CAPD), the manufacturer recommends increasing the dosing interval to every 48 hours. For patients on HD, the dose should be administered immediately after the HD session.[28] Patients undergoing continuous renal replacement (CRRT) should receive the regular dose every 24 hours since CRRT removes a significant amount of daptomycin.[68,69]

The recommendation to dose every 48 hours creates a practical problem for patients receiving HD. Since most patients receive HD three times a week (eg, Monday, Wednesday, and Friday) rather than every other day, discordance in days for daptomycin administration and HD session occurs after the 72 hour HD-free period (ie, between Friday and Sunday). While some clinicians administer daptomycin three times weekly after each dialysis session, a recent Monte Carlo simulation demonstrated that dosing at 4–6 mg/kg decreased exposure during the last third of the 72 hour HD-free period.[70] The study suggested that supplementing a post-HD dose before the 72 hour period by 50% achieved daptomycin exposure similar to patients with normal renal function receiving daptomycin every 24 hours. Whether this dosing strategy is safe to apply in patients receiving doses higher than 6 mg/kg is unknown.

Monitoring Parameters

Creatinine clearance should be assessed at baseline and regularly monitored to optimize dosing of daptomycin, especially in patient with fluctuating renal function. As daptomycin resistance has developed during treatment of severe infections, daptomycin susceptibility should be performed at baseline and repeated when treatment failure is suspected.

Because of the potential for its occurrence during daptomycin therapy, patients should be monitored for signs and symptoms of skeletal muscle toxicity. In particular, CPK should be monitored at baseline and at least once a week until cessation of therapy. Patients potentially at increased risk for muscle toxicity include those receiving high-dose therapy, concomitant or recent use of HMG-CoA reductase inhibitor, or renal impairment. More frequent monitoring of CPK may be necessary. Per manufacturer's recommendation, the criteria for discontinuation of daptomycin are CPK elevation >5 times ULN

ITT			MC			Confirmed MRSA		
D	C	*P*	D	C	*P*	D	C	*P*
382/534 (71%)	397/558 (71%)	NS	309/456 (84%)	309/365 (85%)	NS	21/28 (75%)	25/36 (69%)	NS
–	–	–	–	–	–	15/15 (100%)	30/30 (100%)	NS
36/48 (75%)	42/45 (88%)	NS	27/37 (73%)	32/39 (82%)	NS	24/31 (77%)	27/28 (96%)	CI* (–35.3, –2.8)

Notes: #Standard therapy included vancomycin or penicillinase-resistant penicillin; ^Patients were allowed to be switched to penicillinase-resistant penicillin if MRSA was not isolated; *Significant difference noted (expressed as confidence interval, no *P*-value given).
Abbreviations: RCT, randomized controlled trial; D, Daptomycin; ST, standard treatment; V, vancomycin; C, comparator; *P*, *P*-value; NS, Not significant; —, not evaluated; CE, clinically evaluable; BID, twice a day; ITT, intention to treat; MC, microbiological cure; CI, confidence interval.

with presentation of symptoms of muscle toxicity, or CPK elevation >10 times ULN, with or without symptoms.[28]

Patient Preference

Daptomycin is only available as an IV formulation, similar to standard treatment options for treatment of cSSSI in hospitalized patients. Unlike vancomycin, daptomycin does not require periodic blood draws for therapeutic drug monitoring. Daptomycin is administered as a short, 30-minute infusion once a day for patients with Clcr > 30 mL/min. In contrast, standard treatments such as nafcillin and vancomycin are typically administered multiple times a day, or as a continuous infusion.[2,71] Because of these properties, daptomycin may be an attractive selection for outpatient parenteral antibiotic therapy. Postmarketing analysis of patients receiving outpatient parenteral antibiotic therapy has shown daptomycin to safe and effective.[72]

Place in Therapy

Daptomycin has shown to be rapidly bactericidal with excellent in vitro activity against Gram-positive organisms that cause cSSSI, including multi-drug resistant organisms. Efficacy in treating cSSSI and tolerability has been demonstrated in both comparative and postmarket analyses in adults, including the elderly population. While beta-lactam antibiotics still maintain superb activity against many Gram-positive pathogens that cause cSSSI (MSSA, β hemolytic streptococci, and *E. faecalis*), they lack activity against resistant pathogens such as MRSA. Vancomycin, although active against resistant bacteria, has been increasingly implicated in treatment failures for severe MRSA infections. As such, daptomycin plays a role in the treatment of cSSSI. In fact, daptomycin is an acceptable initial treatment for ABSSI based on the MRSA practice guideline established by the Infectious Diseases Society of America.[3]

Comparative studies thus far have not shown superiority of daptomycin vs. standard treatment for cSSSI, despite its excellent in vitro activity. While some studies suggest faster clinical improvement with daptomycin as compared to standard therapy, the data is conflicting and more robust studies are needed. Lastly, the acquisition cost of daptomycin is much more expensive than standard therapy.[53] However, routine therapeutic drug monitoring is not necessary for daptomycin, as compared to vancomycin.

Based on data currently available, daptomycin should be reserved for treating infections where there is confirmed or high suspicion of resistance, allergy, or intolerability to standard treatment. Because of the potential for cross-resistance with vancomycin, daptomycin MICs should be checked before starting therapy if possible. Regardless of using daptomycin or standard treatment, timely surgical intervention should be performed if warranted, since severe infections with high bacterial burden without proper intervention have increased risk for treatment failure.

Table 5. Summary of effectiveness in postmarketing analyses from CORE and EU-CORE databases.

Study	Database date range	Patient population	Daptomycin therapy	Overall response rate*	Response rate for cSSSI*
Chamberlain et al[56]	CORE 2007	Patients with post-surgical infections n = 104	Median 5.5 mg/kg (3.8 to 8.5) Duration: 14 days (1 to 85)	91% (95/104)	91% (95/104)
Moise et al 2008[57]	CORE 2005–2007	Patients who received high dose daptomycin CE: n = 74 cSSSI: n = 22	Median Dose: 8 mg/kg (8 to ≥12) Duration: 15 days (1 to 90)	89% (66/74)	88% (15/22)
DePestel et al[58]	CORE 2005–2007	Patients over 65 yo n = 844 ABSSSI: n = 284 (65.8% were cSSSI); CE: n = 241	Median Dose: 5.6 mg/kg (4.0 to 6.0) Duration: 14 days (5 to 28)	90% (764/844)	92% (223/241) *Note: all ABSSSI*
Owens et al[59]	CORE 2004	Patients with ABSSSI n = 522 cSSSI: n = 334	Median Dose: 4 mg/kg (2.3 to 12) Duration: 12 days (1 to 148)	97% (504/522)	96% (319/334)
Gonzales-Ruiz et al[60]	EU-CORE 01/2006–68/2008	Patients on daptomycin therapy n = 1127 cSSSI: n = 373	Dose: 6 and 4 mg/kg most common Median duration Inpatient: 10 days (1 to 246) Outpatient: 13 days (2 to 189)	79% (893/1127)	81.2% (303/373)

Note: *Defined as clinical cure or improvement.
Abbreviations: CORE, Cubicin Outcomes Research and Experience; EU-CORE, European Cubicin Outcomes Research and Experience; CE, clinically evaluable; cSSSI, complicated skin and skin structure infections; ABSSSI, acute bacterial skin and skin structure infections.

Conclusions

With its unique mechanism of action, daptomycin is an antibiotic active against MRSA that has been shown to be efficacious in treatment of cSSSI. Daptomycin serves as a viable alternative to standard therapy to treat patients with cSSSI, especially those infected with multi-drug resistant organisms including MRSA. In addition, daptomycin should be considered when allergy or intolerance to standard treatment is suspected. While daptomycin must be administered intravenously, its convenient once daily dosing appeals for use in both the inpatient and outpatient settings when other options are unfeasible.

Author Contributions

Wrote the first draft of the manuscript: MJ. Contributed to the writing of the manuscript: MJ, JL. Agree with manuscript results and conclusions: MJ, JL. Jointly developed the structure and arguments for the paper: MJ, JL. Made critical revisions and approved final version: MJ, JL. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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