Daptomycin: A Review 4 Years after First Approval

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Key Words

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Abstract

Daptomycin is the first approved member of a new class of antibiotics, namely the cyclic lipopeptides. Daptomycin has rapid bactericidal activity against Gram-positive pathogens. It acts by penetrating into the bacterial cell wall with consecutive formation of pores, loss of electrical membrane potential and inhibition of peptidoglycan synthesis. As the mode of action of daptomycin is 'concentration-dependent', the pharmacokinetic/pharmacodynamic indices that correlate best with its activity are the ratios of the peak concentration (C_{max}) to minimum inhibitory concentration (MIC) or the area under the curve (24-hour AUC) to MIC. Daptomycin should be administered intravenously once daily, because adverse effects on skeletal muscle associated with an increase in plasma levels of creatine phosphokinase and myopathy were observed more frequently at shorter dosing intervals. Overall, the rate of adverse events during daptomycin therapy is comparable to that of other standard regimens. Daptomycin was shown to be not inferior to antimicrobial standard therapy and therefore was approved for complicated skin and skin structure infections at a dose of 4 mg/kg, for *Staphylococcus aureus* bacteremia and right-sided endocarditis at a dose of 6 mg/kg. Dosage regimens remain a mat-

ter of discussion, and an increase in the currently approved doses from 4–6 to 6–8 mg/kg per day for severe infections seems promising. Though not approved up to now, daptomycin appears to be a treatment alternative for Gram-positive bone and joint infections based on clinical observations. Large international studies showed high susceptibility of relevant Gram-positive pathogens to daptomycin, even in multidrug-resistant strains. Thus, treatment of infections caused by Gram-positive cocci resistant to other antimicrobial drugs is a potential indication of daptomycin. Since glycopeptides and daptomycin have the same target site, there appears to be a risk of reduced susceptibility to both drugs after consecutive use. Therefore, daptomycin should be used with caution for treatment of vancomycin-resistant isolates or after prior vancomycin (glycopeptide) therapy. This review describes the history, mechanism of action, susceptibility, recent discoveries and clinical experience regarding daptomycin, discussing its current role in the field of infectious diseases.

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Introduction and History

Daptomycin is the first approved member of an old class of antibiotics, the cyclic lipopeptides. It is a 13-amino acid compound which is derived from fermentation by a nonribosomal peptide synthetase mechanism of *Strep-*

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Fig. 1. Structure of daptomycin.

tomyces roseosporus [1]. The compound was discovered by Eli Lilly and Company in the 1980s and designated LY 146032, dapcin or cidecin in earlier years. Daptomycin showed promise in 19 phase 1 and two phase 2 clinical studies which were conducted in the 1980s and early 1990s involving more than 370 subjects [2]. Unexpected treatment failures which occurred in patients with bacteremia and endocarditis were attributed to inadequately low doses, suggesting higher dosing [3, 4]. However, reversible adverse effects on skeletal muscle, including elevated creatine phosphokinase (CPK) levels, muscle weakness, and myalgia were reported after dosing every 12 h. Overall, Eli Lilly was not satisfied with the clinical results observed with the twice-daily dosing regimens utilized in these studies and ceased further research activities. In 1997, worldwide development and commercialization rights to daptomycin were acquired by Cubist Pharmaceuticals. New attempts to investigate and develop daptomycin were favored by the dramatically increasing emergence of bacterial resistance among Gram-positive bacteria in the 1990s, like methicillin-resistant *Staphylococcus aureus* (MRSA). The pronounced trend towards higher resistance rates of clinically important bacterial species essentially contributed to reassessment of the benefit-risk ratios of new antimicrobial agents. Moreover, it was discovered that once-daily dosing of daptomycin in dogs, though leading to higher peak levels, causes significantly less frequent CPK increase and myopathy than thrice-daily dosing [5]. Thus, it turned out that skeletal-muscle effects are minimized if the total daily dose is administered as one single short infusion every 24 h [5]. Following successful phase 3 studies, daptomycin was approved for treatment of complicated skin and skin structure infections (SSSI) in the United States of America in

November 2003 at a dose of 4 mg/kg of body weight under the trade name Cubicin®. Since 2006 daptomycin is marketed in several European Union member states by Novartis Pharmaceuticals following its acquisition of Chiron Pharmaceuticals, which previously held European licenses. Currently, daptomycin is going to be approved also for therapy of *S. aureus* blood stream infections at a dose of 6 mg/kg.

Chemistry and Mode of Action

Daptomycin is a cyclic 13-residue lipopeptide, namely N-decanoyl-L-tryptophyl-D-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-threo-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine-lactone (fig. 1). It is provided for clinical purposes as lyophilized powder for the preparation of infusion solution [6].

The suggested mechanism of action consists of daptomycin insertion into the Gram-positive bacterial cytoplasmic membrane, whereas Gram-negative bacteria are not affected, probably due to their outer membrane [7]. A number of hydrophobic moieties are clustered at one end of the daptomycin molecule, while neutral polar and anionic residues are localized at the other end, leading to amphipathicity of the molecule. These features suggest a mode of action in which the large hydrophobic cluster of the lipopeptide interacts with the acyl chain region of the bacterial membrane. The interaction of daptomycin with the bacterial membrane is calcium-dependent. Calcium ions neutralize the anionic charges and favor association with the membrane head groups. Calcium binding increases the amphipathicity and the solvent-exposed hydrophobic surface [8]. Upon association with lipid membranes, daptomycin undergoes calcium-dependent conformational changes [8]. Once inserted into the membrane significant perturbations ensue, including lipid flip-flop [8]. The binding of calcium ions also causes the core decapeptide lactone to draw inwards. This not only facilitates further drug penetration into the membrane but also results in oligomerization of the daptomycin peptide. Oligomerization is followed by disruption of the functional integrity of the cytoplasmic membrane with formation of pores, triggering membrane leakage, release of intracellular ions and rapid cell death [7]. In addition, it was observed in *Bacillus megaterium* that active transport of cell wall amino acids, as well as formation of sugar-peptide precursors and peptidoglycans are inhibited by disruption of the transmembrane electrochemical

gradient [9]. Jung et al. [8], in contrast, provided evidence that membrane depolarization occurs after cell death and is a consequence rather than a cause of the bactericidal activity of daptomycin. However, daptomycin has bactericidal activity, and bacterial killing by daptomycin is greater when the organism is exposed to the drug while in logarithmic growth than in stationary growth phase [4]. However, in contrast to other antimicrobial agents, the killing rates achieved with daptomycin during stationary growth are remarkably high [10].

Pharmacodynamic animal studies indicated that daptomycin has a concentration-dependent mode of action. This means that efficacy of daptomycin is best correlated with its peak concentration (C_{max}) or 24-hour area under the concentration versus time curve (AUC) in relation to the minimum inhibitory concentration (MIC) of the bacterial strain, rather than with the time the drug concentrations exceed MIC (time above MIC) [11–13]. In mice, the C_{max} /MIC ratios (using total drug concentrations) required for a bacteriostatic effect against *S. aureus* isolates ranged from 59 to 94, while the 24-hour AUC/MIC ratios to achieve bacteriostasis ranged from 388 to 537. It is appropriate to apply the required magnitude of these indices obtained in mice to humans, because the extent of protein binding is identical in both species [12]. Thus, for humans the mean total C_{max} values of $99 \pm 12 \mu\text{g/ml}$ [14] and 24-hour AUC values of $598 \pm 110 \mu\text{g} \times \text{h/ml}$ [15] measured at doses of 6 mg/kg can be related to the MICs inhibiting 90% of tested staphylococcal strains (MIC_{90}) of $0.5 \mu\text{g/ml}$ (table 1). According to these indices sufficient drug efficacy can be expected in the majority of patients. If the MICs of infecting strains exceed $0.5\text{--}1 \mu\text{g/ml}$, dose adjustment might be necessary to ensure that target AUCs are achieved.

Garrison et al. [3] evaluated the impact of protein binding on bacterial killing using an in vitro pharmacodynamic model. Serum concentration-versus-time curves of patients receiving 6 mg/kg daptomycin as intravenous infusion were simulated in vitro in the presence and absence of 4% albumin. The average time required for a 99% kill of *S. aureus* was 0.3 h without albumin whereas it was 0.9 h in the presence of albumin. The fact that the presence of protein diminishes bactericidal activity is not surprising as daptomycin has a plasma protein binding of approximately 91.7% [16].

The postantibiotic effect (PAE) is a pharmacodynamic parameter which is defined as the length of time that bacterial growth is suppressed following brief exposure to an antibiotic. Daptomycin staphylococcal PAE ranged from approximately 1.1 to 6.2 h, with a mean of 2.5 h [17,

Table 1. Susceptibility of relevant pathogens to daptomycin

Pathogen	MIC_{90} , $\mu\text{g/ml}$	Reference
MSSA	0.25/0.5	[29]/[37]
MRSA	0.5	[29]/[37]
Coagulase-negative staphylococci	0.5	[37]/[36]
VS <i>E. faecium</i>	2/4	[29]/[37]
VR <i>E. faecium</i>	2/4	[29]/[37]
VS <i>E. faecalis</i>	2	[29]/[37]
VR <i>E. faecalis</i>	4/2	[29]/[37]
Beta-hemolytic streptococci	0.25	[36]
Viridans streptococci	0.5	[36]
<i>S. agalactiae</i>	0.25	[37]
<i>Corynebacterium</i> spp.	0.25	[36]
<i>Listeria</i> spp.	2	[36]

VS = Vancomycin-susceptible; VR = vancomycin-resistant.

18]. The effect of subinhibitory drug levels following supra-inhibitory levels which persist between dosing intervals is referred to as the postantibiotic sub-MIC effect (PA-SME). Staphylococcal PA-SME effects at 0.4 times the MIC ranged from 3.0 h to >12 h [17]. PA-SMEs and PAEs for *S. aureus* and *Enterococcus faecalis* were dose-dependent, and it was concluded that the relatively high PA-SME and PAE values found in vitro support once-daily dosing of daptomycin [17, 18].

Compared to vancomycin or gentamicin, daptomycin was more effective in preventing bacterial adherence to the surfaces of medical devices, and biofilm formation [19, 20]. Moreover, daptomycin was more active in inhibiting bacterial colonization of preexisting biofilms than other antimicrobial drugs [21]. Further in vitro experiments indicated that daptomycin is also active against *S. aureus* and *Streptococcus epidermidis* present in biofilms [19, 20]. These properties suggest its utilization as catheter lock solution. Clinical studies, however, are required to test the in vivo efficacy in this indication.

Synergistic or additive effects against *S. aureus* were observed in vitro between daptomycin plus gentamicin, and additive effects were seen for daptomycin plus rifampicin [22]. Others, in contrast, found that the addition of gentamicin does not enhance the bactericidal activity of daptomycin against staphylococcal and enterococcal isolates [23]. According to in vitro experiments daptomycin plus either rifampicin, oxacillin, or fosfomycin had synergistic effects against the majority of enterococcal strains tested [24, 25]. Surprisingly, daptomycin combined with either oxacillin, ampicillin-sulbactam, ticarcillin-clavu-

lanate, or piperacillin-tazobactam also showed synergy against MRSA [26]. Different explanations for the synergistic effect of these beta-lactams against resistant bacteria have been provided. It was speculated that either daptomycin alters peptidoglycan precursors in a manner that penicillin binding protein 2' might be unable to perform its cross-linking function in the presence of the beta-lactam, or that daptomycin affects the functionality of factors which are essential for methicillin resistance [26]. Alternatively, beta-lactams might enhance the activity of daptomycin. Though in vivo data are still required, these in vitro data indicate that the combination of daptomycin with beta-lactams could be reasonable also in *S. aureus* infections. Up to now, antagonism between daptomycin and other antimicrobial drugs has not been reported.

Exposure of murine macrophages to clinical *S. aureus* isolates in the presence of daptomycin led to a dampened inflammatory response with diminished secretion of tumor necrosis factor and reduced accumulation of inducible oxide synthase protein in comparison with addition of vancomycin or oxacillin [27]. Since excessive production of these inflammatory mediators can contribute to the development of sepsis in infection patients, the impact of this effect deserves further investigation.

Antibacterial Spectrum and in vitro Susceptibility

In general, daptomycin is active against a broad spectrum of Gram-positive bacteria, while there is no activity against Gram-negative pathogens. Activity against distinct anaerobic species was observed. To date, the clinically most relevant pathogens are coagulase-positive and coagulase-negative staphylococci, as well as streptococci and enterococci. Importantly, daptomycin was observed to be active also against a number of pathogens that are resistant to other antibiotics [4, 28].

When performing broth microdilution susceptibility tests calcium must be supplemented in order to obtain correct results. The activity of daptomycin is enhanced two- to fourfold by increasing the calcium concentration in Mueller-Hinton broth from the usual in vitro concentration of 20–25 to 50 mg/l, a level which closely approximates ionized calcium levels in human serum [29, 30]. For most pathogens the breakpoint of susceptibility is defined by an MIC of ≤ 1 $\mu\text{g/ml}$, whereas *E. faecalis* isolates are considered susceptible if the MIC is ≤ 4 $\mu\text{g/ml}$ [31].

In spite of calcium substitution, testing of *S. aureus* strains by disk diffusion failed to detect strains catego-

rized as nonsusceptible by the microdilution method [32–34]. Thus, disk diffusion tests do not provide reproducible results and are therefore currently not recommended for susceptibility testing of daptomycin. Consequently daptomycin disks were removed from the market by Cubist Pharmaceuticals and the respective disk diffusion breakpoints were removed from the CLSI M100 standard in 2006 [35].

In contrast, the epsilon test (Etest) method using daptomycin strips with calcium supplementation (AB Biodisk, Solna, Sweden) provided a relatively good correlation with results of broth microdilution (95% of values within ± 1 $\log_2$ dilution) [34]. However, among selected strains identified as nonsusceptible by broth microdilution, 9.8% of tested isolates were classified as susceptible by Etest. This discrepancy was in part attributed to the lack of an intermediate range for classifying daptomycin susceptibility [34]. Nevertheless, the Etest was judged to be a reliable method by different study authors [32, 34]. Regardless of the method used for susceptibility testing, we recommend careful clinical and microbiologic monitoring if the MIC values of treated strains are close to the breakpoint.

Large multicenter studies investigating the clinically most relevant pathogens in Europe, North and South America showed that all staphylococcal and >95% of enterococcal isolates, including glycopeptide-susceptible and -resistant enterococci as well as MRSA were susceptible to daptomycin in vitro (table 1) [29, 36, 37]. The MICs inhibiting 90% of tested strains (MIC₉₀) were 0.25–0.5 $\mu\text{g/ml}$ for staphylococcal and streptococcal isolates, and 2–4 $\mu\text{g/ml}$ for enterococcal isolates [29, 36, 37]. Multidrug-resistant isolates were defined as concurrent resistance to three or more agents from different classes. In multidrug-resistant and non-multidrug-resistant isolates of *S. aureus*, enterococci, and *S. pneumoniae*, there was no major difference in the MIC distributions of daptomycin, i.e. modal MICs ≤ 1 doubling dilution.

Importantly, isolates of *Streptococcus pyogenes*, *Streptococcus agalactiae*, streptococci of groups C and G, viridans streptococci and *Listeria monocytogenes* were susceptible to daptomycin in vitro, independent of vancomycin or methicillin resistance [38]. Susceptibility of less frequent Gram-positive pathogens *Erysipelothrix rhusiopathiae*, *Corynebacterium* spp., *Abiotrophia/Granulicatella* sp., *Rothia mucilaginosa* and *Gemella morbillorum* was reported, with MIC values ranging from ≤ 0.125 to 2 $\mu\text{g/ml}$ [39]. Daptomycin was active in vitro also against some Gram-positive anaerobes including *Clostridium perfringens*, *Clostridium difficile*, *Peptostreptococcus* spp.,

Eubacterium spp., *Propionibacterium* spp., *Leuconostoc* spp., *Finegoldia magna* and *Pediococcus* spp. [28, 40–42]. In contrast, daptomycin had decreased activity against *Actinomyces*, *Clostridium ramosum*, *Eubacterium lentum* and *Lactobacillus plantarum* strains [42].

Pharmacokinetics

Daptomycin pharmacokinetics (PK) follows a two-compartment model in plasma with first-order elimination [14, 43, 44]. In healthy volunteers daptomycin PK is linear and dose-proportional at doses up to 12 mg/kg [45]. The distribution phase is not complete until 4–6 h after administration. At steady state, after 7 daily doses of 6 mg/kg, mean plasma elimination half-life was 8.9 ± 1.3 h in healthy volunteers [14]. The volume of distribution was 0.104 ± 0.013 liters/kg, corresponding with a predominantly extracellular distribution and high protein binding. The concentrations of ^{14}C -labeled daptomycin were much higher in plasma than in whole blood, indicating that little of the drug crosses into erythrocytes [15]. In plasma the mean AUC from zero to infinity ($\text{AUC}_{0-\infty}$) was $747 \pm 91 \mu\text{g} \times \text{h/ml}$, C_{max} was $98.6 \pm 12.0 \mu\text{g/ml}$ at steady state (doses of 6 mg/kg). Plasma protein binding is reversible and approximates 91.7% [16]. Protein binding was not concentration-dependent at daptomycin concentrations between 2.5 and 80 $\mu\text{g/ml}$ [16]. Daptomycin is mainly excreted by the kidneys, with a plasma clearance (CL) of about 7–9 ml/h/kg and a renal CL of 4–7 ml/h/kg. Importantly, metabolism by liver microsomes is limited, with only minimal involvement of the cytochrome P-450 isoenzymes [15].

In order to identify factors contributing to interindividual variability of daptomycin PK, a population PK analysis was performed with data from 15 clinical trials considering over 30 covariates [46]. Daptomycin plasma CL was a function of renal function, body temperature and sex. Of these, renal function contributed most significantly to interindividual variability. While drug CL varied linearly with the estimated creatinine CL, the relationship to sex and temperature was of doubtful impact. Concluding, this analysis supported dosing on a milligram per kilogram body weight basis with suggested modified regimens only for patients with severe renal disease.

Impact of Age, Obesity and Drug Abuse

A single-dose study compared the PK of daptomycin in young (18–30 years) versus old (≥ 75 years) healthy vol-

unteers, detecting higher values of $\text{AUC}_{0-\infty}$ and terminal half-life in the older group [43]. This was interpreted as a result of changes in renal function, i.e. impaired renal CL in subjects ≥ 75 years of age. No differences were observed for C_{max} and the volume of distribution. It was concluded that no dose adjustment is necessary only due to age. A study in children and adolescents ≤ 18 years is currently being performed in the United States of America.

A more recent study showed that in moderately obese and morbidly obese subjects, absolute volumes of distribution and plasma CL of daptomycin were higher compared to matched nonobese controls [47]. Drug exposure was increased in obese subjects, as expressed by an approximately 25% increase in C_{max} and an approximately 30% increase of AUC in plasma compared to nonobese controls. Thus, dosing based on body weight results in higher C_{max} and AUC values in obese subjects [48]. However, this increase was well within the range that was previously determined to be safe and well tolerated, and study authors concluded that no dose adjustment is required for morbidly obese patients [47].

In intravenous drug abusers peak serum concentrations were observed to be lower than in healthy volunteers [4]. It was speculated that this finding may be attributed to the descriptively higher renal drug CL in drug abusers. Alternatively the descriptively larger volume of distribution found in drug abusers was reported as a possible cause of lower drug serum concentrations. The reasons for the larger volume of distribution and higher renal CL in intravenous drug abusers, however, were unclear.

Penetration into Deep Compartments

The penetration of daptomycin into cantharidin-induced inflammatory blister fluid in healthy volunteers was investigated by Wise et al. [49]. The mean peak concentrations were 77.5 $\mu\text{g/ml}$ in plasma versus 27.6 $\mu\text{g/ml}$ in inflammatory fluid, with terminal elimination half-lives of 7.74 and 13.2 h, respectively. The mean ratio of 24-hour AUC in inflammatory fluid to that in plasma was 0.68, suggesting good penetration into inflammatory bodily fluids. The relatively high drug concentrations in blister fluid in spite of high plasma protein binding (approximately 90%) could be explained by the considerable amount of protein in blister fluid, where also remarkable drug amounts are bound.

Daptomycin passes the blood-brain barrier only to a small degree. In experimental meningitis in rabbits, penetration of daptomycin was between 4.4 and 7.5%. Pene-

tration into inflamed meninges was higher than into noninflamed meninges (2%) within the first 8 h [50]. According to the authors daptomycin at a dose of 15 mg/kg was clinically and microbiologically more effective in experimental meningitis than a standard regimen with ceftriaxone plus vancomycin [50, 51]. Daptomycin doses used in the meningitis model, however, were quite high, and it is too early at this stage to apply the rabbit data to clinical practice.

Dosing Regimens

Dosing of daptomycin is based on individual body weight. Daptomycin is currently approved at a dose of 6 mg/kg of body weight for therapy of *S. aureus* bacteremia, including right-sided endocarditis, and a dose of 4 mg/kg for complicated skin and skin structure infections. Since daptomycin has a concentration-dependent mode of action (i.e. its efficacy depends on $C_{\max}$ or AUC), and in order to reduce adverse side effects the entire daily dose should be administered as one single intravenous short infusion. In addition, once-daily administration might favor patient compliance, compared to agents requiring multiple daily doses. It was reported that daptomycin was safe also if administered as a bolus of 6 mg/kg over 2 min [52], which also might promote its use for outpatient parenteral antibiotic therapy of community-acquired infections. Adverse events possibly related to bolus injection were dizziness and headache.

In patients with severe or terminal renal insufficiency (creatinine CL <30 ml/min) and in subjects undergoing hemodialysis or peritoneal dialysis daptomycin should be used cautiously because elimination half-life and AUC are increased by two- to threefold. If creatinine CL is <30 ml/min dosing intervals should be extended to 48 h, with administration after dialysis if possible. For patients receiving continuous renal replacement therapy the daptomycin dose should be the same as recommended for patients with a creatinine CL <30 ml/min [53].

A matched controlled study in patients with moderate liver impairment showed similar PK parameters as in the healthy group after a single dose of 6 mg/kg total body weight [44]. Since metabolization by liver microsomes is marginal, patients with moderate hepatic impairment (Child-Pugh class B) do not require adjustment of daptomycin dose regimen.

Clinical experience with 1 patient and a study involving 12 healthy volunteers indicate that doses of 12 mg/kg can be administered over ≥ 14 days without any toxicity

[45, 54]. Although currently this dosing regimen cannot be recommended, these experiences illustrate that higher doses are indicated in select cases and that such doses might be approved in the future (e.g. 6–8 mg/kg for deep-seated staphylococcal infections). Moreover, higher doses are expected to impede emergence of bacterial resistance.

Efficacy in Different Indications

Severe Skin Infections

The efficacy of daptomycin for treatment of SSSI was investigated in large international clinical trials [55]. A total number of 1,092 patients with SSSI including wound infections, abscesses, diabetic and other ulcers were randomized to receive either daptomycin at a dose of 4 mg/kg once daily or standard therapy. Standard therapy consisted of either cloxacillin, oxacillin, nafcillin, flucloxacillin, or, if risk of MRSA was suspected, vancomycin. Success of treatment was defined as clinical cure, disappearance of infection signs and symptoms or improvement. Nine hundred and two patients were evaluable and therapeutic equivalence was found with an overall success rate of 83.4% for daptomycin, and of 84.2% for the control group. Both groups were equivalent with regard to the distribution of the pathogens methicillin-susceptible *S. aureus* (MSSA), MRSA, *S. pyogenes*, *S. agalactiae*, and *Streptococcus dysgalactiae*. Though not being a main outcome variable, clinical success occurred more rapidly with daptomycin than with comparable drugs, with success rates on day 7 of 63 vs. 33%, respectively. A prospective study with randomization to either daptomycin or comparable antibiotic (vancomycin or semisynthetic penicillin) for SSSI by Lipsky and Stoutenburgh [56] showed essentially the same result, i.e. clinical and microbiological success rates were equivalent.

Bacteremia and Endocarditis

The effect of daptomycin (6 mg/kg of body weight) in the therapy of bacteremia and endocarditis caused by *S. aureus* was investigated in a randomized clinical trial in comparison with standard therapy [57]. In the control group an antistaphylococcal penicillin plus gentamicin were used for the treatment of MSSA, while vancomycin was utilized against MRSA. This trial in 246 patients demonstrated noninferiority of daptomycin for treatment of *S. aureus* right-sided endocarditis and *S. aureus* bacteremia in both the intention-to-treat population and in the patient group with documented adherence to the

protocol. For the intention-to-treat population, overall success rates were 44.2% in the daptomycin group and 41.7% in the control group. Subgroup analysis showed a descriptive advantage of daptomycin for MRSA, and a descriptive advantage of standard therapy for MSSA. Daptomycin had a nonsignificantly higher rate of microbiologic failure (15.8%), with isolation of *S. aureus* strains becoming less susceptible to daptomycin during treatment in 7 of 19 patients. Low success rates in both groups were observed for left-sided endocarditis (1 of 9 patients in the daptomycin group, 2 of 9 patients in the standard therapy group). The overall rate of adverse events was lower in the daptomycin group without reaching statistical significance. Renal dysfunction occurred in 11.0% of patients who received daptomycin and in 26.3% of patients who received standard therapy ($p = 0.004$), a finding essentially attributed to the thrice-daily administration of gentamicin to patients who were randomized to the control group. Limitations of the clinical trial were the short follow-up period of 42 days after therapy completion, and the relatively small number of cases of endocarditis (64 cases of endocarditis among 246 patients, of these 18 cases of left-sided endocarditis).

A retrospective review was performed of 31 patients with Gram-positive bacteremia or infective endocarditis who received daptomycin therapy at doses of 4–6 mg/kg intravenously based on the practitioner's discretion [58]. Eleven patients had MRSA, 11 patients had vancomycin-resistant enterococci, and 7 patients had MSSA infection. Clinical resolution was achieved in 24 patients (77%), including all MRSA patients. Seven patients died, six of whom had vancomycin-resistant enterococci.

The Cubicin Outcomes Registry and Experience (CORE) is a multicenter retrospective observational chart review of daptomycin patient outcomes. The CORE group reported 61 patients with non-catheter-related bacteremia who were treated with daptomycin [59]. Of these, 46% received concurrent antibiotic therapy, mostly beta-lactams. Overall, clinical success defined as improvement or cure was achieved in 79%.

There is limited data about the application of daptomycin in neutropenic bacteremia with vancomycin-resistant *Enterococcus faecium*, where cure was achieved with daptomycin in 4 of 9 patients [60]. A case of pacemaker-induced *S. aureus* mitral valve acute bacterial endocarditis with persistent bacteremia from a coronary stent was cured with prolonged high-dose daptomycin therapy 12 mg/kg for 41 days without occurrence of any toxicity [54]. Successful 6-week treatment of *Corynebacterium striatum* endocarditis with daptomycin plus rifampicin was

reported in a woman with hemodialysis-dependent chronic renal failure [61].

Bone and Joint Infections

CORE retrospectively analyzed 67 patients with osteomyelitis treated with daptomycin after therapy [62]. Median therapy duration was 35 days (range 1–546 days) with a mean initial dose of 5.3 mg/kg. Out of 67 patients 42 (63%) were cured, 13 patients improved. Failure was observed in 7 patients, 5 were nonevaluable. There was a trend towards higher failure rates (27%) for doses ≤ 4 mg/kg, compared to doses >4 mg/kg with a failure rate of $\leq 7\%$. It was concluded that daptomycin may be useful for osteomyelitis, but that further prospective trials are necessary to properly answer this question.

Moreover, CORE retrospectively analyzed 26 of 31 patients after treatment for septic arthritis [63]. The mean daptomycin treatment duration was 29 days. Eighty-eight percent had received another antibiotic prior to daptomycin. The change to daptomycin was performed in most cases due to allergy or intolerance of vancomycin. Fifty percent received concomitant antibiotics in addition to daptomycin. Cure was observed in 58%, improvement in 38% of patients. No failure occurred in patients with Gram-positive pathogens, the only failure was observed in a case where the infection turned out to be caused by Gram-negative pathogens in the culture. Another retrospective analysis of 9 patients diagnosed with Gram-positive bone and joint infection showed that 8 were successfully treated [64], indicating that joint infections may become an indication for daptomycin therapy.

Twelve patients with Gram-positive prosthetic joint infection, who could not receive vancomycin, were prospectively monitored [65]. All completed a 6-week course of daptomycin. At follow-up after 7–13 months 6 patients had no clinical, laboratory or radiographic signs of recurrence. In 1 patient the first course failed and hardware removal was performed. Five patients had failure due to MRSA confirmed by culture. The authors concluded that effectiveness of daptomycin in prosthetic joint infection is uncertain, especially when hardware is retained.

Mixed Indications

Finally, CORE retrospectively reviewed outcomes of 810 patients with differently located infections receiving daptomycin [66]. Of these, 56% had SSSI, 18% had bacteremia, 13% had osteomyelitis. Seventy-six percent had received other antibiotics prior to daptomycin. Daptomycin doses were 4 mg/kg in 51% and ≥ 6 mg/kg in 37% of

patients. Overall, 92% of patients achieved clinical success, defined as improvement or cure. Highest success rates were detected in SSSI (95%) and osteomyelitis (93%). Lower success rates were described for foreign body infections (88%) and endocarditis (76%). In the data set that was analyzed success rates were independent of the applied dose. In patients with impaired renal function (creatinine CL <30 ml/min) success rates were lower (82%) than in patients with a creatinine CL $\geq$ 30 ml/min (94%). However, reduced renal function might only reflect the higher risk and morbidity of these patients.

Pneumonia

Phase III clinical trials were conducted for the treatment of hospitalized patients with community-acquired pneumonia. Despite potent bactericidal activity against *S. pneumoniae* in vitro, daptomycin failed to achieve superiority over ceftriaxone (79 vs. 87% efficacy) in humans [67]. Failure to treat bronchial-alveolar pneumonia by *S. pneumoniae* was observed in a mouse model of infection [67], whereas it was assessed to be as efficient as vancomycin in a hamster pneumonia model using *S. aureus* [68]. In vitro experiments showed that daptomycin interacts with pulmonary surfactant, resulting in inhibition of antibacterial activity. This interaction is specific to daptomycin and consistent with its mechanism of action. Daptomycin irreversibly inserts into the surfactant aggregates, resulting in sequestration of the antibiotic, rendering it inactive [67]. These experiments do not answer some crucial questions such as, how is daptomycin eliminated from the lung when bound to surfactant? Is its accumulation in surfactant saturable? Thus, daptomycin is currently not recommended for monotherapy of pneumonia and subsequent studies are necessary to clarify these open questions. However, the situation appears to be different for abscesses in the lung caused by *S. aureus* where surfactant is not expected to interact with the drug to a relevant degree.

Summarizing this entire section, therapeutic equivalence of daptomycin in comparison with standard antibiotics was proven for Gram-positive SSSI and *S. aureus* bacteremia and right-sided endocarditis. Though definitive evidence from randomized trials is missing, there is data to support daptomycin as a useful treatment option for Gram-positive prosthetic valve and pacemaker infections, as well as for osteomyelitis and joint infections. Data on urinary tract and foreign body infections is scarce, but daptomycin might be eligible in some cases. From the available data, it is tempting to speculate that daptomycin may also be adequate for treatment of intra-

abdominal abscesses or diabetic foot infections in combination with other antimicrobial agents. This, however, needs to be confirmed by clinical studies.

Emergence of Daptomycin Resistance

A study was performed in vitro to determine the emergence of bacterial resistance using serial passages in daptomycin-containing broth and chemical mutagenesis [69]. The selected mutants had MICs which were 8- to 32-fold higher than for the parental strain. These MIC increases were considered relatively modest, comparable to previous findings for other antimicrobial drugs. MIC increases were stable during repeated passages in the absence of drug. There were mutants with normal growth rates, with reduced growth rates and with severe growth defects. Daptomycin remained bactericidal against all mutants at 8 times the MIC. These mutants did not demonstrate cross-resistance to vancomycin or ampicillin. Some mutants with increased MICs partly lost virulence in vivo [69, 70]. In an animal model, emerging resistance was created by administering suboptimal doses (1.5 mg/kg), whereas continued bactericidal activity persisted at doses of 6 and 10 mg/kg, confirming the importance of adequately high dosing regimens [71].

Lately, clinical cases of emerging nonsusceptibility during daptomycin therapy were observed for *E. faecium* [72], methicillin-resistant *S. epidermidis*, methicillin-resistant *Streptococcus sanguis* (our own clinical observations), and MRSA [73–75], especially after prolonged drug exposure. Based on the increase of MICs during therapy observed in some cases, it was concluded that daptomycin susceptibility should be monitored during therapy [76], and that dosing should be adequately high. In spite of modestly rising MICs patients were treated successfully with daptomycin, if the medical management was adequate [77]. On the other hand, 1 case of decreased bacterial killing by daptomycin was described for a breakthrough isolate in spite of unchanged MICs [78].

Special attention was raised by the clinical observation of reduced staphylococcal susceptibility to daptomycin after prior vancomycin treatment, e.g., in a case with prosthetic joint infection and bacteremia caused by MRSA [79]. In this patient *S. aureus* persisted in repeated blood cultures during prolonged courses of vancomycin despite susceptibility to vancomycin as well as to daptomycin. However, after prolonged consecutive daptomycin therapy, susceptibility to both vancomycin and daptomycin decreased. Clinical cases of decreasing suscepti-

bility of *S. aureus* to vancomycin by antibiotic pressure of daptomycin treatment or vice versa, associated with clinical treatment failure, were reported by various groups for differently located infection sites [33, 80–83]. Similar clinical observations were reported for enterococcal infections [72, 84]. These findings were explained by the shared target of vancomycin and daptomycin. Although daptomycin and vancomycin have different mechanisms of action, both agents act on the bacterial cell wall. Staphylococcal cell wall thickening induced by prolonged exposure to vancomycin acts as a physical barrier to both daptomycin and vancomycin penetration of the cell, increasing the MICs of both antimicrobials [80]. The relative molecular weights of daptomycin (1,620.67) and of vancomycin (1,485.7) are comparatively high. A direct correlation between reduced daptomycin susceptibility, vancomycin resistance and cell wall thickening could be established in 53 *S. aureus* strains. This observation was confirmed by genetic investigations proving that the levels of proteins which form part of the bacterial response to inhibition of peptidoglycan biosynthesis change similarly after exposure to either vancomycin or daptomycin [85]. Typical changes in the peptidoglycan composition occur in strains developing resistance to either vancomycin or daptomycin, i.e. a reduction in O-acetylation, which could lead to hydrophobicity and altered substrate properties towards cell wall-lytic enzymes [86].

In MRSA daptomycin has the same clinical success rates as in MSSA [57]. Thus, with the exception of vancomycin, reduced susceptibility to daptomycin by prior administration of other antimicrobial drugs has not been reported. Consequently, daptomycin is not the first therapeutic choice for treatment of *S. aureus* infections if reduced susceptibility to vancomycin (or teicoplanin) is suspected or documented [87]. Clinicians also should be aware of the fact that daptomycin has to be used with caution after failure of prolonged vancomycin therapy, even in vancomycin-susceptible pathogens.

Safety

The most frequent adverse events according to the manufacturer are anemia, constipation, diarrhea, nausea, vomiting, local injection site reactions, and headache. Less frequent, but important, are adverse effects on skeletal muscle which may appear as increases in CPK (MM isoenzymes), muscle pain, muscle weakness, or myositis during therapy, up to rhabdomyolysis. Among 534 patients with complicated SSSI receiving 4 mg/kg of dap-

tomycin once daily 0.2% of the study population reported myopathy [55], which resolved after drug discontinuation [55, 88]. Muscle pain may also occur without pronounced CPK elevation, apparently resolving after discontinuation [89]. Rates of drug-related CPK increase were 2.1% (n = 11 of 534 patients) in the daptomycin group and 1.4% (n = 8 of 558 patients) in the control group receiving standard therapy [55]. In healthy volunteers with once-daily dosing, only slight CPK increases with normalization of CPK values during ongoing therapy were observed [14]. Severe myopathy after once-daily daptomycin administration was described in 1 case, where daptomycin was started after discontinuation of simvastatin [90] and in another case during combined administration with voriconazole [91]. The mechanisms of skeletal muscle toxicity of daptomycin in humans are not known up to now. In dogs CPK increase correlated with alterations in muscle fibers, with a maximum on day 8 [5]. The heart muscle was histologically not affected in dogs [5]. A toxicodynamic study revealed that probability of CPK increase after 14 days of treatment is more likely (0.51) if trough levels are ≥ 25.7 mg/l, while being much lower (0.06) if trough levels are < 25.7 mg/l [92]. Measuring of daptomycin trough levels, however, is not a routine procedure. The overall incidence of severe myopathy might seem acceptable, for instance in comparison with that of HMG-CoA reductase inhibitors, where its frequency is estimated to be 0.1% [93]. Nevertheless, before start and during daptomycin therapy weekly monitoring of CPK levels is recommended, with more frequent testing in cases of unexplained CPK elevations. According to the manufacturer daptomycin should be discontinued in patients with unexplained signs of myopathy in conjunction with CPK elevation $> 1,000$ U/l, or in patients without marked symptoms who have marked elevations in CPK (≥ 5 - to 10-fold upper normal limit). Concomitant therapy with drugs that also may cause myopathy, rhabdomyolysis or CPK elevation should be avoided. For instance, consideration should be given to temporarily suspending the use of HMG-CoA reductase inhibitors, or cyclosporin during daptomycin therapy. The clinical combination of daptomycin plus fluoroquinolones, which also have a potential of causing tendopathy and myopathy, has not been investigated yet. Therefore, we suggest special precaution in this regard.

Peripheral neuropathy and renal insufficiency during daptomycin therapy were reported, however, the link with daptomycin is not clear. Possible hepatotoxicity, ending after discontinuation of daptomycin, was observed in 1 case [88]. If Gram-negative infections occur

during daptomycin therapy they are obviously not covered by daptomycin therapy. A case of daptomycin-induced eosinophilic pneumonia was reported [94]. There are no data available concerning daptomycin in pregnancy. However, in animal experiments there was no evidence of harmful effects on pregnancy, prenatal development, birth, and postnatal development.

Overall, in the two large clinical trials the rate of side effects was equivalent to that of standard therapy [55, 57], with a nonsignificantly higher rate of adverse effects in the standard therapy group in one of these studies [57], essentially due to renal disorders caused by the addition of gentamicin. High-dose daptomycin administration of 12 mg/kg per day for 41 days to 1 patient and to 12 healthy volunteers over 14 days was not associated with any toxicity [45, 54].

Summary

Daptomycin belongs to a new class of cyclic lipopeptide antibiotics with rapid bactericidal activity against Gram-positive pathogens. Due to drug penetration into the bacterial cell wall consecutive formation of pores occurs with impairment of peptidoglycan synthesis and loss of the electrical membrane potential.

Daptomycin should be administered only once daily, because severe adverse effects were observed more frequently if infusions were administered every 8 or 12 h. A once-daily daptomycin administration regimen is also supported by its 'concentration-dependent' activity. Accordingly, the pharmacokinetic/pharmacodynamic indices that correlate best with its activity are the ratios of C_{max} to MIC and 24-hour AUC to MIC. Administration once daily suggests the use of daptomycin for outpatient parenteral antibiotic therapy of community-acquired infections. Dosing is performed according to body weight (4–6 mg/kg) and has to be adjusted in patients with impaired renal function. Dosage of daptomycin is still a matter of discussion, and an increase in the currently approved doses from 4–6 to 6–8 mg/kg per day appears reasonable for severe infections due to recent clinical data.

Daptomycin is not inferior to standard therapy and is approved for the treatment of SSSI at a dose of 4 mg/kg and for *S. aureus* bacteremia and right-sided endocarditis at a dose of 6 mg/kg. It seems to be a treatment alternative also for bone and joint infections caused by Gram-positive cocci, whereas it is not recommended for pneumonia due to drug inactivation by surfactant. Treatment of in-

fections caused by Gram-positive strains resistant to other antimicrobial drugs may be an important indication of daptomycin. Though not approved, daptomycin might be considered also for pacemaker prosthetic valve or joint infections, osteomyelitis, or in patients requiring prolonged antibiotic therapy who have received linezolid for 28 days, as linezolid therapy is approved for a maximum period of 28 days only. Daptomycin should be used with caution for treatment of vancomycin-resistant isolates or after prior vancomycin therapy because glycopeptide antibiotics and daptomycin have the same target site, bearing the risk of reduced susceptibility to both drugs after consecutive use. If daptomycin is applied for mixed infections involving Gram-negative pathogens (e.g. diabetic foot) it has to be combined with an appropriate antimicrobial drug.

The rate of adverse effects is comparable to other standard antibiotics. The most important adverse effect during daptomycin therapy is increase in CPK levels in plasma and myopathy [5]. Therefore, at least weekly monitoring of CPK levels is recommended during therapy. Concomitant therapy with drugs that are associated with myopathy, rhabdomyolysis or CPK elevations should be avoided.

Large international studies in general showed high susceptibility of relevant Gram-positive pathogens to daptomycin, even in multidrug-resistant strains. Promising clinical results suggest that the use of daptomycin may be expanded to additional indications. In an era of emerging bacterial resistance to established antibiotics, daptomycin turns out to be a valuable treatment option for infections caused by Gram-positive pathogens.

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