Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

New Drug

Daptomycin: A Cyclic Lipopeptide Antimicrobial Agent

LilyAnn Jeu, PharmD,[1] and Horatio B. Fung, PharmD, BCPS[2]

[1]*Pharmacy Service, and* [2]*Critical Care Center, VA Medical Center, Bronx, New York*

ABSTRACT

Objectives: The aims of this article were: to summarize the pharmacology, pharmacokinetics, and efficacy of daptomycin; to explore its safety profile; and to discuss its current and potential roles as an antimicrobial therapy.

Methods: A literature search was conducted using the MEDLINE (1966–August 2004) and International Pharmaceutical Abstracts (1970–August 2004) databases with the search terms *daptomycin*, *LY146032*, and *lipopeptide antibiotics*. Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy and documents submitted to the US Food and Drug Administration were also reviewed.

Results: Phase III study results suggest no difference in efficacy or tolerability between daptomycin 4 mg/kg IV QD and vancomycin or semisynthetic penicillins for complicated skin and skin-structure infections. Animal studies suggest daptomycin may be useful for the treatment of endocarditis. Daptomycin is not indicated for pneumonia, with poorer outcomes than conventional treatment. It is available as an IV medication and exhibits 92% plasma protein binding in vitro. In healthy adult humans, daptomycin has a volume of distribution of 0.1 L/kg and a plasma elimination half-life of ~9 hours, and is eliminated primarily by renal excretion (~54%). In patients with reduced renal function, including those receiving hemodialysis and peritoneal dialysis, the dose interval should be 48 hours. No dosage adjustment appears to be necessary for mild to moderate hepatic impairment. The use of daptomycin in patients with severe hepatic impairment has not been assessed. The most commonly reported adverse events include constipation, nausea, injection-site reactions, headache, and diarrhea. Patients should also be monitored regularly for skeletal muscle toxicity.

Conclusions: Daptomycin may be useful for complicated skin and skin-structure infections and gram-positive pathogens resistant to conventional antimicrobials. However, limited data are currently available for duration of treatment beyond 14 days and at doses >4 mg/kg QD. (*Clin Ther.* 2004;26:1728–1757) Copyright © 2004 Excerpta Medica, Inc.

Key words: daptomycin, LY146032, lipopeptide antibiotic, gram-positive resistance, skin and skin-structure infections.

Accepted for publication September 13, 2004.

doi:10.1016/j.clinthera.2004.11.014
0149-2918/04/$19.00

INTRODUCTION

Challenging the treatment of infections due to gram-positive pathogens is the development of resistance to currently available agents.[1,2] Vancomycin has traditionally been used to treat infections caused by oxacillin-resistant or methicillin-resistant *Staphylococcus aureus* (ORSA or MRSA, respectively); strains with reduced susceptibility to vancomycin (minimum concentration to inhibit 90% growth [MIC_{90}], 8 µg/mL), termed vancomycin-intermediate *S aureus* (VISA),[3–5] have appeared since 1996.[5–7] In addition, 3 clinical cases of vancomycin-resistant *S aureus* (VRSA) (minimum inhibitory concentration [MIC], ≥32 µg/mL) in the United States have been detected since 2002.[6–11] Increasing resistance to vancomycin among enterococcal strains has also been a growing concern.[12–14]

Use of newer antimicrobials such as linezolid and quinupristin-dalfopristin for treatment of nosocomial infections attributed to vancomycin-resistant strains has revealed new resistance problems as well. Linezolid-resistant enterococci have appeared since the drug was first used in patients receiving linezolid for vancomycin-resistant *Enterococcus faecium* (VREF) infections.[9,15–17] In addition, in 2002, a linezolid-resistant clinical strain of *S aureus* was identified.[18] Resistance to linezolid has been associated with use of the agent for at least 3 to 4 weeks.[15,18] Furthermore, linezolid-resistant VREF (LRVREF) strains have also been identified in patients with[19] and without prior treatment with linezolid.[16,20,21] In addition, current estimates suggest that the incidence of resistance to quinupristin-dalfopristin in *E faecium* is ~4% worldwide compared with 14% reported in the United States.[2] The SENTRY Antimicrobial Surveillance Program data for the years 1997 through 2000[22] have also found that susceptibility to quinupristin-dalfopristin decreased in the United States from 92% in the year 1999 to 83% in 2000.

Clearly, changes in the susceptibility profile of gram-positive pathogens have escalated the need for more innovative drugs. This article reviews the pharmacology, efficacy, and safety of daptomycin.*[23,24] Early studies investigating the use of daptomycin were conducted by Eli Lilly and Company (Indianapolis, Indiana) until Cubist Pharmaceuticals, Inc., obtained worldwide marketing rights for daptomycin and submitted its own investigational new drug application to the US Food and Drug Administration (FDA) in December 1998.[23] Daptomycin received marketing approval from the FDA in September 2003 for the treatment of complicated skin and skin-structure infections caused by susceptible gram-positive pathogens including *S aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subspecies *equisimilis*, and vancomycin-susceptible *Enterococcus faecalis*.[24] Because daptomycin use continues to be investigated in ongoing trials for other indications, the present review also discusses its potential place in therapy.

Daptomycin, the first of a new class of antibiotics, is an acidic cyclic lipopeptide antibiotic. It is the *N*-decanoyl analog of the A21978C lipopeptide factor C1, one of 3 fermentation products of the A21978C complex, produced by *Streptomyces roseosporus*.[25] Daptomycin is characterized by a cyclic 13–amino acid anionic nucleus and an amide-linked lipophilic 10–amino acid fatty acyl side chain[26] (**Figure 1**).[24] All analogs of A21978C have the 13–amino acid core, which contains unique amino acids (eg, L-kynurenine and 3-methyl glutamine acid) and a lactone bond in the ring.[25] Antimicrobial activity requires at least 4 to 8 carbons in the fatty acyl side chain, with longer chains showing greater antimicrobial activity. After chemical and enzymatic modification of A21978C, daptomycin (ie, LY146032) demonstrated the best combination of in vitro antimicrobial activity against selected gram-positive cocci and the least acute toxicity in mice (median lethal dose, 600 mg/kg IV) among structural derivatives synthesized.[25] The chemical name for this compound is *N*-decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine$_{\varepsilon 1}$-lactone. Daptomycin has an empiric formula of $C_{72}H_{101}N_{17}O_{26}$ and a molecular weight of 1620.67 kDa.[24]

The purposes of this article were as follows: to review the pharmacology, pharmacokinetics, and in vitro and in vivo efficacy of daptomycin; to explore the safety profile of this first agent in a new class of antimicrobials; and to discuss its current and potential roles as an antimicrobial therapy.

*Trademark: Cubicin® (Cubist Pharmaceuticals, Inc., Lexington, Massachusetts).

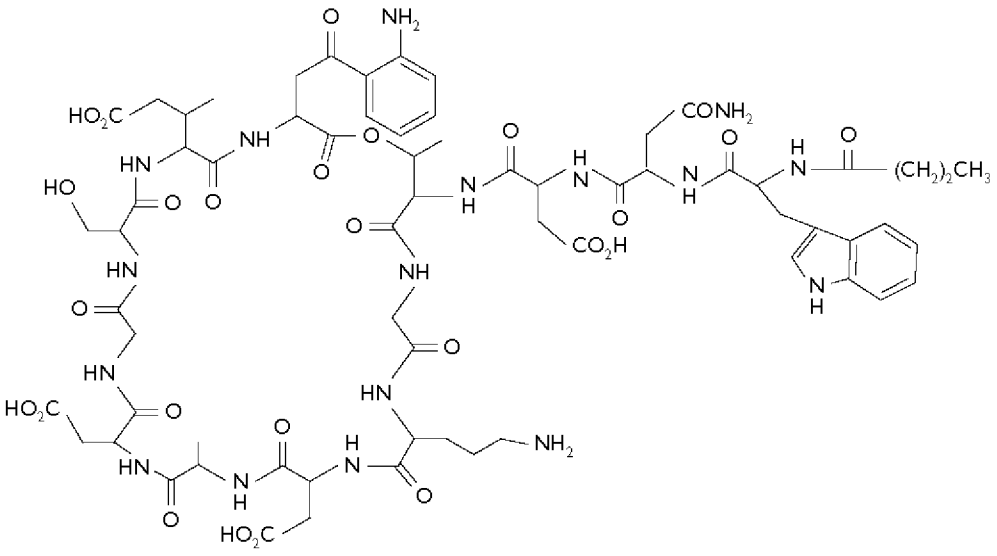

Figure 1. Structural formula of daptomycin.[24]

MATERIALS AND METHODS

A literature search was conducted using the MEDLINE (1966–August 2004) and International Pharmaceutical Abstracts (1970–August 2004) databases and abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy. Key search terms included *daptomycin*, *LY146032*, and *lipopeptide antibiotics*. References were also obtained through screening of citations identified in articles gathered. In addition, information was obtained from the FDA Web site, which contained documents submitted to the FDA in support of the new drug application for daptomycin.

MECHANISM OF ACTION

Daptomycin appears to disrupt the membrane potential of bacterial cell membranes (**Figure 2**).[27] After binding to phospholipid vesicles in the planar bilayer membrane,[28–30] daptomycin inserts the acyl fatty acid chain into the bacterial cytoplasmic membrane, triggering oligomerization of membrane proteins to form ion channels, transmembrane pores, or other aggregate structures across the plasma membrane.[31] Although the initial binding occurs independently of calcium,[30] daptomycin requires physiologic concentrations of calcium (50 mg/dL in vitro) to reduce microbial viability.[32] Conformational changes in the core decapeptide lactone, induced by binding of calcium ions, increase its amphiphaticity and reduce the charge, allowing daptomycin to interact with neutral or acidic membranes.[33] The presence of calcium ions promotes further insertion of the daptomycin tail into the phospholipid layer. Exposure of the hydrophobic surface facilitates penetration and the oligomerization step.[34]

Formation of transmembrane structures disrupts the membrane integrity, resulting in leakage of intracellular potassium[28,35] and dissipation of membrane potential in gram-positive pathogens.[31] Antimicrobial activity is associated with a reduction of membrane potential from –165 mV to –100 mV independently of changes in pH or chemical gradient across the cell membrane.[35] Reduction of the electrical potential disrupts the electrochemical gradient–induced proton motive force required for adenosine triphosphate synthesis, which normally plays a role in active transport of nutrients,[35] concentration of amino acids,[36] or formation of nucleotide-linked sugar-peptide precursors of peptidoglycan.[36]

Early studies attempting to delineate the mechanism of action of daptomycin suggested it may inhibit the biosynthesis of lipoteichoic acid, one of the constituents of the plasma membrane,[37] or peptidoglycan components in gram-positive bacteria.[28] Studies with *E faecium* protoplasts, which lack a peptidoglycan layer, supported the hypothesis that daptomycin

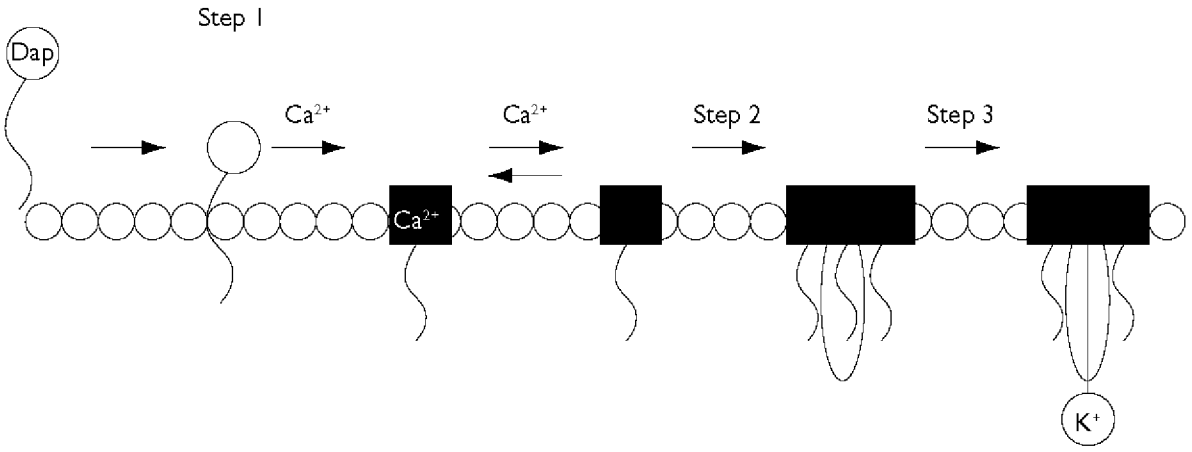

Figure 2. Proposed mechanism of action for the bactericidal effects of daptomycin. Step 1: Insertion of daptomycin (Dap) into the bactericidal cytoplasmic membrane in a calcium (Ca^{2+})-dependent fashion. Step 2: Oligomerization and disruption of the functional integrity of the cytoplasmic membrane. Step 3: Release of intracellular ions, leading to cell death. Adapted with permission.[27]

inhibits the production of lipoteichoic acid as its primary mechanism of action, with the secondary result of inhibition of peptidoglycan synthesis.[38] Although this hypothesis was further supported by accumulation of lipoteichoic acid precursors, as detected using thin-layer chromatography,[39,40] a more recent study revealed that daptomycin remains bactericidal even in the absence of ongoing lipoteichoic acid synthesis.[41]

Regardless of the mechanism of action, scanning electron microscopy reveals the induction of abnormal features (eg, antler-like protrusions, ghosts, blebs, deep web-like fissures) or structures (eg, filamentous growth, linear cells, miniature cells) in the cell surface after daptomycin treatment.[42,43] These morphologic changes are believed to be associated with production of defective cell wall material, and they appear to occur independently of the calcium-mediated intracellular penetration of daptomycin at target sites.[42]

PHARMACOKINETICS

Daptomycin pharmacokinetics have been studied in vitro, in animals, and in healthy human adults. There have also been a few case reports describing daptomycin pharmacokinetics in adults with infections. After IV administration, daptomycin undergoes distribution in a 2-compartment model[44] and elimination primarily by renal excretion. Values for pharmacokinetic parameters are indicated as mean or mean (SD) values, unless otherwise indicated. Pharmacokinetic parameters for doses between 3 and 8 mg/kg every 24 hours are summarized in **Table I**.[44,45]

In Vitro Pharmacokinetics

Pharmacokinetic studies in vitro show daptomycin exhibits 91% to 96% plasma protein binding (mean, 94%) when added to whole serum at concentrations of 2.5 to 80 µg/mL[46]; serum samples from healthy human subjects show ~90% plasma protein binding.[46] In particular, 85.0% to 95.5% of daptomycin binds to albumin, as expected for an acidic compound, and 25.0% to 40.1% of daptomycin may also bind to $alpha_1$-acid glycoprotein at in vitro concentrations of 5 to 80 µg/mL.[44] At 2.5 µg/mL, daptomycin shows no detectable binding to $alpha_1$-acid glycopeptide. Based on MICs (13 µg/mL for total bound and unbound drug) for *S aureus* and one enterococcus strain described by Woodworth et al,[44] pharmacokinetic studies suggest daptomycin should be administered at clinical doses of at least 4 to 6 mg/kg.

The high degree of protein binding may account for the therapeutic failure observed in early clinical studies conducted by Eli Lilly and Company (as cited by Lee et al[46]), because the serum concentration of unbound drug may not sufficiently exceed the MIC to inhibit bacterial growth. For example, the MIC for total (ie,

Table I. Mean (SD) values for pharmacokinetic parameters of daptomycin at selected doses in healthy adult volunteers.*

Daily Dose	C_{max}, µg/mL	C_{ss}, µg/mL	AUC, µg·h/mL	$T_{1/2}$, h	V_d, L/kg	Systemic Clearance, mL/min per kg	Renal Clearance, mL/min per kg
3 mg/kg							
Single dose[44]	41.55 (7.48)	ND	329 (46.9)	8.35	0.11 (0.02)	0.16 (0.02)	0.05 (0.02)
4 mg/kg							
Single dose[44]	52.25 (5.85)	ND	382 (72.7)	8.56	0.13 (0.01)	0.18 (0.03)	0.07 (0.02)
Multiple doses[45]	54.6 (5.4)	57.8 (3.0)	494 (75)	8.1 (1.0)	0.10 (0.01)	0.14 (0.02)	1.05 (0.31)†
6 mg/kg							
Single dose[44]	82.0 (20.4)	ND	598 (110)	8.06	0.12 (0.02)	0.17 (0.03)	0.06 (0.02)
Multiple doses[45]	86.4 (7.1)	98.6 (12)	747 (91)	8.9 (1.3)	0.10 (0.01)	0.14 (0.02)	1.00 (0.23)†
8 mg/kg							
Multiple doses[45]	116.3 (10.1)	133.0 (13.5)	1130 (117)	9.0 (1.2)	0.10 (0.01)	0.12 (0.01)	0.68 (0.11)†

V_d = apparent volume of distribution; ND = no data.
*n = 6 for each treatment group.
†Unbound drug.

bound plus unbound) daptomycin for *S aureus* is 5 µg/mL, whereas the MIC for unbound daptomycin alone is 0.25 µg/mL. For enterococcal strains, MIC for total drug is 10 µg/mL, whereas MIC for unbound drug is 0.5 µg/mL.[46] When comparing pharmacokinetics of total drug versus unbound drug, the mean (SD) C_{max} for a 3-mg/kg dose, occurring 30 minutes after infusion, is 30.3 (10.4) µg/mL for total drug compared with 5.4 (3.3) µg/mL for the unbound fraction. After 12 hours, the concentration of the unbound fraction decreases to 0.37 µg/mL. By 24 hours after infusion, the concentration of the unbound fraction further decreases to <0.15 µg/mL, well below the MIC of the targeted pathogens mentioned previously.[46]

Animal Studies

In mice, daptomycin shows 91% to 92.5% plasma protein binding and a linear increase in dose and C_{max} or AUC with increasing doses from 1-, 2.5-, 5-, 10-, 15-, and 20-mg/kg doses.[47] Linear pharmacokinetics have been observed even at 40-mg/kg doses, which is associated with a peak concentration of 207 µg/mL and an AUC of 375 µg·h/mL.[48] Daptomycin 10 mg/kg BID in rabbits yields a steady-state C_{max} (66.4 [18.0] µg/mL) similar to that in humans who receive 3 mg/kg IV BID and trough concentration of 16.8 (6.6) µg/mL after 8 or 12 hours.[49] Daptomycin 25 or 40 mg/kg QD in rats achieves similar blood concentrations in humans at doses of 4 or 6 mg/kg QD, respectively.[50] Mean peak concentrations in rats after 2 hours were 64 and 91 µg/mL, respectively, and concentrations were undetectable by 24 hours.

In a model of inflammatory methicillin-sensitive *S aureus* and MRSA[51] (ie, infected rabbits were treated with daptomycin 20 or 50 mg/kg), the mean peak concentration of daptomycin in the fibrin clot core had an ~40% lower concentration and took 3 hours longer to achieve compared with the peak concentration at the periphery of the clot. The AUC of the clot was also significantly higher in periphery than in the core for each dose tested ($P < 0.05$). Mean (SD) AUC in serum was also greater than in the fibrin clots for daptomycin 20 mg/kg (575 [36.7] µg/g per hour vs 215 [6.2] µg/g per hour) or daptomycin 50 mg/kg (1089 [39.9] µg/g per hour vs 326 [16.8] µg/g per hour). Thus, limited diffusion of daptomycin into fibrin clots, such as those in vegetations in endocarditis, may limit treatment success. Among guinea pigs infected with *Streptococcus epidermidis* in a tissue-cage model for device-related infections, daptomycin 5 mg/kg BID produced a C_{max} of 6.3 µg/mL and C_{min} of 3.8 µg/mL after 4 days of treatment.[52]

Human Studies

After administration of a single dose of daptomycin in clinically studied doses (eg, 3–8 mg/kg), the appar-

ent volume of distribution (V_d) in humans ranged from 0.10 to 0.13 L/kg and may have been affected by a high degree of protein binding (90%–95%) and large molecular size.[24,44] Daptomycin exhibits linear accumulation at doses from 0.5 to 6 mg/kg. Pharmacokinetics of distribution are consistent with a 2-compartment model, because completion of the distribution phase occurs 4 to 6 hours after administration of daptomycin. Overall, daptomycin shows limited total body clearance at a rate of 0.13 to 0.21 mL/min per kg at doses of 2, 3, 4, or 6 mg/kg via IV infusion.[44] Renal clearance accounts for 34% to 54% of total systemic clearance.[44]

Daptomycin pharmacokinetics have also been studied in a double-blind, multiple-dose, dose-escalating, QD regimen among 24 healthy male and female adults treated with daptomycin for 7 to 14 days.[45] For treatment doses between 3 and 6 mg/kg per dose, daptomycin showed linear pharmacokinetics and ~20% nonlinearity in pharmacokinetics when the dose was increased to 8 mg/kg (highest dose studied to date). For example, after 7 days of treatment, doubling of the dose from 4 mg/kg to 8 mg/kg resulted in a 2.2-fold increase in the AUC and C_{max} rather than a predicted 2-fold increase in AUC or C_{max} (mean [SD] AUC, 494 [75] µg·h/mL vs 1130 [117] µg·h/mL; mean [SD] C_{max}, 57.8 [3.0] µg/mL vs 133.0 [13.5] µg/mL). After 7 doses, the $T_{1/2}$ was estimated to be ~9 hours and the V_d was calculated to be 0.1 L/kg. Systemic clearance occurred at a rate of 0.14 mL/min per kilogram (reported as 8.2 mL/h per kg) with ~54% of the dose excreted intact in urine.[45]

In 3 healthy male volunteers (18–45 years old and within 15% of ideal body weight) treated with a single dose of ^{14}C-Trp-labeled daptomycin (1 mg/kg via IV for 1 dose),[44] 99% of labeled compound (ie, daptomycin and metabolites) were recovered from urine and fecal samples within the first 4 days. Approximately 83% of radiolabeled daptomycin was recovered in the urine (78%) and feces (5%) over 9 days, whereas only trace amounts of labeled compound were recovered in breath or saliva. Daptomycin was the only radiolabeled compound identified in plasma, but only 51.7% of labeled compound recovered in the urine was daptomycin, suggesting that daptomycin may undergo renal metabolism.

Furthermore, in the comparison of pharmacokinetics of radiolabeled ^{14}C-compound (1 mg/kg IV infusion) and unlabeled daptomycin (0.5–6 mg/kg), similar degrees of accumulation and extent of exposure (mean [SD] C_{max}, 13.3 [3.1] µg/mL for labeled compound vs 12.8 [1.7] µg/mL for unlabeled daptomycin; mean [SD] AUC, 96.0 [7.4] µg·h/mL vs 96.1 [2.3] µg·h/mL, respectively) and systemic clearance (mean [SD] 0.19 [0.02] mL/min per kg vs 0.19 [0.01] mL/min per kg, respectively) were noted. However, different rates of renal clearance (mean [SD] 0.14 [0.01] mL/min per kg for the labeled compound vs 0.09 [0.01] mL/min per kg for daptomycin) further support the hypothesis that daptomycin may be renally metabolized, in addition to renally eliminated, or that tryptophan may be reabsorbed for protein synthesis.[44]

Few studies of daptomycin pharmacokinetics have been conducted in patients with infections. In a model of canthadrin-induced inflammation, penetration of daptomycin into inflammatory fluid was investigated.[53] Only 68.4% of daptomycin (4 mg/kg IV) penetrated the inflammatory fluid, with a mean (SD) C_{max} of 27.6 (9.5) µg/mL after 3.67 hours. Within 24 hours, mean (SD) AUC was 318.2 (84.9) µg·h/mL. The half-life of daptomycin in inflammatory fluid was highly variable, ranging from 6.3 to 32 hours, with a mean time of 17.3 hours. In comparison, volunteers treated with daptomycin 4 mg/kg IV without inflammation showed a mean (SD) AUC of 468.0 (15.6) µg·h/mL over 24 hours, a mean (SD) C_{max} of 77.5 (8.3) µg/mL, and a $T_{1/2}$ of 7.7 hours.[53] This degree of accumulation is similar to that in rats with inflammatory fluid.[54] At 30 mg/kg in inflammatory fluid in rats, daptomycin produced a C_{max} of 141 µg/mL after 1 hour and an AUC of 558 µg·h/mL over a 24-hour period, only slightly higher than the AUC reported in inflammatory fluid of human volunteers.[53]

In one case report, a 29-year-old, HIV-positive male received daptomycin 2 mg/kg QD for 5 days for cellulitis and thrombophlebitis caused by group A beta-hemolytic streptococci.[55] The apparent V_d was estimated to be 0.102 to 0.123 L/kg and the elimination $T_{1/2}$ was determined to be 9.1 hours after the first dose and then 7.2 hours after the fifth dose. Daptomycin was cleared at rates of 14.2 and 13.7 mL/min/1.73 m^2 after the first and fifth doses, respectively. After the first dose, ~70% of the dose was renally excreted unchanged (11.1 mL/min/1.73 m^2). However, after the fifth dose, 28% of the dose was renally excreted unchanged (4.4 mL/min/1.73 m^2). Although

this dose is no longer recommended for treatment,[24] a study of the pharmacokinetics of daptomycin 2 mg/kg in healthy adults at steady state yielded similar mean (SD) values for V_d (0.108 [0.014] L/kg), systemic clearance (0.168 [0.034] mL/min per kg or 11.76 [2.38] mL/min for a 70-kg patient), renal clearance (0.103 [0.018] mL/min per kg or 7.21 [1.26] mL/min), and mean $T_{1/2}$ (7.40 hours).[56]

Among 6 IV drug abusers (IVDAs) receiving treatment with daptomycin (loading dose 6 mg/kg, then 3 mg/kg every 12 hours) for gram-positive endocarditis, cellulitis, or bacteremia, the peak concentration was lower (mean [SD] C_{max}, 35.45 [8.26] μg/mL vs 59.2 [9.3] μg/mL; $P < 0.005$) and V_d at steady state was greater (mean [SD], 0.21 [0.03] L/kg vs 0.16 [0.5] L/kg; $P < 0.01$) for the IVDAs compared with 6 healthy volunteers in historical data for patients given the same regimen of daptomycin.[57] Although no other differences in pharmacokinetic parameters were detected for this patient sample, observed differences may be associated with the relatively low serum albumin (mean, 2.9 mg/dL; range, 2.0–3.8 mg/dL) among the IVDAs.

Pharmacokinetics in Special Populations

Using data collected from 282 participants in 15 clinical trials, Dvorchik et al[58] evaluated sources of interindividual variability in an analysis of daptomycin population pharmacokinetics. Patients received daptomycin 4 to 8 mg/kg QD for up to 14 days. Overall, the model confirmed that daptomycin distribution and clearance follows a 2-compartment model with first-order elimination. A linear relationship was determined between the V_d in the peripheral compartment and intercompartmental clearance and body weight, supporting the dosing of daptomycin on a milligram-per-kilogram basis. Renal function, sex, and body temperature were factors found to affect daptomycin kinetics. In particular, renal function was the single most important factor, reducing variability by 18.9% (from 52.1% to 33.2%) in the Bayesian estimate of pharmacokinetic parameters. For patients with similar degrees of renal function, female patients showed clearance rates at 80% of those exhibited by male patients, although there is no recommendation for dosage adjustment.[24] In addition, although body temperature >37.2°C was cited as a potential source of variability, the authors did not provide statistical details on its impact and cautioned readers about interpreting this result because only 14% of subjects had body temperatures ≥38°C. Factors not found to contribute to daptomycin clearance included the presence of comorbid diseases (ie, diabetes mellitus, ascites or edema, hypertension, or heart failure) or concomitant use of medications that are actively secreted in the renal tubule or that are highly protein bound.

Renal Insufficiency

To date, 2 abstracts[59,60] and 1 published report[58] describe the pharmacokinetics of daptomycin in patients with varying degrees of renal function. Patients were categorized according to creatinine clearance (CrCl) level or by those with end-stage renal disease requiring hemodialysis or peritoneal dialysis. Results from these pharmacokinetic studies are summarized in **Table II**.[58–60] In the small-scale study (N = 44) reported by Sica et al,[60] statistically significant differences (although level of significance was not reported) were found for plasma clearance and $T_{1/2}$ between patients with CrCl ≤40 mL/min and those receiving dialysis compared with other groups with CrCl >40 mL/min. When compared with the AUC for patients with CrCl ≥80 mL/min, the AUC ratio was 2.34 for patients with CrCl ≤40 mL/min, 2.31 for patients receiving hemodialysis, and 2.78 for patients receiving peritoneal dialysis. Thus, in accordance with FDA recommendations for the evaluation of pharmacokinetics in patients with reduced renal function (ie, no dosage adjustment required for AUC ratio 80%–125%, or C_{max} ratio 70%–143% of comparison group), the authors suggested the daptomycin dose should be adjusted for patients with CrCl ≤40 mL/min. Similar results were also reported in another analysis using different definitions of renal insufficiency (N = 33).[59] Reduced plasma clearance and prolonged $T_{1/2}$ were found among patients with severe renal disease (ie, CrCl <30 mL/min or those receiving hemodialysis), although the level of statistical significance was not reported. Based on these results,[59] daptomycin dosage should be adjusted in patients with CrCl ≤30 mL/min.

In the population pharmacokinetic model that incorporated data from 282 participants,[58] the $T_{1/2}$ of daptomycin was 2.3 times longer in patients with CrCl ≤40 mL/min and 3.5 times longer in those

Table II. Mean values of daptomycin pharmacokinetic parameters in patients with varying degrees of renal function.

Reference	Dosage	C_{max}, µg/mL	AUC, µg·h/mL	Plasma clearance, mL/h per kg	V_d, L/kg	$T_{1/2}$, h
Dvorchik et al[58]*	4–8 mg/kg IV QD × 1–14 d					
CrCl, mL/min						
≥80 (n = 165)		ND	400.8	11.5	0.13	8.3
>40 and <80 (n = 80)		ND	436.5†	8.5†	0.12	9.1†
≤40 (n = 16)		ND	716.2†‡	4.9†‡	0.14	19.0†‡
Dialysis (n = 21)		ND	1205.6†‡§	3.2†‡	0.14	29.3†‡§
Dvorchik et al[59]	4 mg/kg IV × 1 dose over 30 min					
CrCl, mL/min						
≥80 (n = 7)		52.6	517.9	12.1	ND	11.6
≥50 and <80 (n = 4)		54.8	697.9	8.2	ND	15.3
≥30 and <50 (n = 5)		55.7	570.9	8.6	ND	10.3
<30 (n = 6)		47.7	1281.9	4.6‖	ND	29.4‖
ESRD/HD (n = 6)		39.7‖	1254.4	4.2‖	ND	32.8‖
Peritoneal dialysis (n = 5)		51.3	1474.2	3.4‖	ND	31.3‖
Sica et al[60]	4 mg/kg IV × 1 dose over 30 min					
CrCl, mL/min						
≥80 (n = 7)		53.7	531	7.8	0.12	11.7
>40 and <80 (n = 12)		57.5	561	7.6	0.11	10.7
≤40 (n = 7)		48.9	1241	3.3¶	0.13	27.9¶
ESRD/HD (n = 13)		40.3	1224	3.0¶	0.15¶	36.7¶
Peritoneal dialysis (n = 5)		51.5	1474	2.8¶	0.15	31.7¶

V_d = apparent volume of distribution; CrCl = creatinine clearance; ESRD/HD = end-stage renal disease/hemodialysis; ND = no data.
*Median values reported in study. Values for plasma clearance and V_d were divided by median body weight (75 kg) to facilitate comparison of results between studies.
†$P < 0.05$ versus patients with CrCl ≥80 mL/min.
‡$P < 0.05$ versus patients with CrCl >40 and <80 mL/min.
§$P < 0.05$ compared with patients with CrCl ≤40 mL/min.
‖Statistically significant difference from other groups, although level of significance not defined in the study.
¶Statistically significant difference from groups with CrCl >40 mL/min, although level of significance not defined in the study report.

receiving dialysis than among those with CrCl ≥80 mL/min. AUC values were also 1.8-fold and 3.0-fold greater, respectively (**Table II**). Although AUC and mean $T_{1/2}$ also differed between subjects with CrCl ≥80 mL/min and those with CrCl between 40 and 80 mL/min, differences were <10% and were determined by the study authors to be clinically insignificant. Thus, as recommended previously, adjustment of the daptomycin dose should be considered for patients with CrCl ≤40 mL/min.

Hepatic Insufficiency

In a single-dose, parallel-design, matched-controlled (body weight, age, sex) study, the pharmacokinetics of daptomycin were compared in patients with moderately impaired hepatic function (Child-Pugh Class B; n = 10; 7 male subjects) versus healthy volunteers (n = 9; 6 male subjects).[61] All participants received daptomycin 6 mg/kg IV over 30 minutes. No significant differences in pharmacokinetic parameters were found between hepatically impaired and healthy subjects: mean C_{max}, 113.7 µg/mL and 118.3 µg/mL, respectively; mean $T_{1/2}$, 9.0 and 9.4 hours, respectively; mean AUC, 867.4 µg·h/mL and 928.0 µg·h/mL, respectively; and mean V_d at steady state, 0.08 L/kg for both groups. There were no differences in degree of protein binding, fraction of dose excreted in urine, or rate of urinary clearance. Based on this study, no dosage of daptomycin is recommended for patients with moderate hepatic impairment.

Geriatric Patients

A comparison of pharmacokinetics was conducted among 12 healthy adults aged >75 years and 12 adults between the ages of 18 and 30 years. Results showed that total clearance of daptomycin was reduced by 35%, whereas mean AUC, C_{max}, and elimination $T_{1/2}$ increased 58%, 4%, and 74%, respectively, among older patients (ie, aged >75 years) who received a single 4-mg/kg dose versus younger adults (ie, aged 18–30 years).[62] The older patient group showed 34.3% mean urinary fraction excreted, whereas the younger group showed 42.6% mean urinary fraction excreted. Statistically significant differences were observed in the extent of exposure, with older patients showing a higher accumulation (mean [SD] AUC from time 0 to infinity, 473.7 μg·h/mL vs 300.6 μg·h/mL; $P < 0.001$). This may be attributed to reduced renal function associated with aging; differences in CrCl were observed between the 2 groups (ie, 57.6 mL/min for older patients vs 94.8 mL/min for younger patients; $P < 0.001$). Rates of adverse reactions were similar in the older and younger patient groups. Overall, daptomycin pharmacokinetics may be affected by renal function rather than by age alone, suggesting that dosage reduction should not be based on age as the sole criterion.[24,62,63]

Obese Patients

Among 6 moderately obese patients (body mass index [BMI], 25–39.9 kg/m^2), mean C_{max} and AUC were 25% and 30% greater, respectively, than among matched nonobese controls who received a single dose of daptomycin 4 mg/kg based on total body weight.[63] In addition, mean total and renal clearance were 18% and 16% greater, respectively. In 6 extremely obese patients (BMI, >40 kg/m^2), mean C_{max} and AUC were increased by 26% and 31%, respectively, versus nonobese adults. In these patients, however, mean total and renal clearance were 46% and 36% greater, respectively, than controls.[63]

Miscellaneous

No studies have been conducted to examine differences in pharmacokinetics according to race or sex. In addition, studies have not been conducted in pregnant or lactating women.

IN VITRO ACTIVITY

Numerous studies delineating the in vitro antibacterial activity of daptomycin have been published. Because daptomycin binds to its molecular target in a calcium-dependent manner,[64] only those studies in which the calcium concentration of the test medium (Mueller-Hinton broth) used for microdilution susceptibility testing was adjusted to mimic the physiologic level of human serum (ie, 50 mg/L)[64] and performed according to the guidelines set by the National Committee for Clinical Laboratory Standards[65] (NCCLS) were selected for this review. To date, no daptomycin susceptibility MIC breakpoints have been established by the NCCLS.[53] Based on in vitro spectrum of activity, in vivo pharmacodynamic studies, and clinical failure analyses of daptomycin, the FDA has proposed a susceptibility breakpoint MIC of <1 μg/mL for *S aureus* and *Streptococcus* species other than *Streptococcus pneumoniae,* and a susceptibility breakpoint MIC of ≤4 μg/mL for vancomycin-susceptible *E faecalis.*[66] The susceptibility interpretive criteria for other organisms have not been defined.

Daptomycin has been tested in vitro against a wide range of clinically important gram-positive bacteria including *S aureus,* coagulase-negative staphylococci, *E faecalis, E faecium, S pneumoniae, S pyogenes, S agalactiae,* viridans group streptococci, and group B and C streptococci.[64,67–74] Critchley et al[70,71] reported the in vitro activity of daptomycin against a total of 12,907 isolates of gram-positive pathogens collected from patient specimens at 50 hospitals in the United States and 40 in Europe during 2000 and 2001. The collection included *S aureus* (2240 isolates; 28.5% oxacillin-resistant [MIC, >4 μg/mL]), coagulase-negative staphylococci (2166 isolates; 61.1% oxacillin-resistant), *E faecium* (813 isolates; 41.0% vancomycin-resistant [MIC, >32 μg/mL]), *E faecalis* (3927 isolates; 2.0% vancomycin-resistant), other *Enterococcus* species (240 isolates; 7.5% vancomycin-resistant), *S pneumoniae* (2028 isolates; 20.4% penicillin-intermediate [MIC, 0.12–1 μg/mL]; 13.2% penicillin-resistant [MIC, >2 μg/mL]), *S agalactiae* (640 isolates), *S pyogenes* (484 isolates), and viridans streptococci (369 isolates).

Regardless of resistance patterns, all staphylococcal and streptococcal isolates were susceptible to daptomycin with an MIC of ≤1 μg/mL. With the exception of an unspecified number of isolates of vancomycin-

sensitive *E faecium* and other non-*faecium*, non-*faecalis* *Enterococcus* species, which were inhibited at 8 µg/mL (mean MIC_{90}, ≤4 µg/mL; range, 0.03–8 µg/mL), all isolates of enterococci were susceptible to daptomycin with an MIC of ≤4 µg/mL.[70,71] Similar results were reported by other investigators.[64,67,69,72–74] The incidence of elevated daptomycin MICs for gram-positive bacteria was low. For example, in the study conducted by Streit et al,[72] only 2 each of the 3202 isolates of *S aureus* and 838 isolates of coagulase-negative staphylococci had an MIC of 2 µg/mL, and almost all (99.9% [797/798]) isolates of enterococci were inhibited by daptomycin at ≤4 µg/mL. It appears that daptomycin has potent in vitro activity against a wide range of clinically important gram-positive pathogens.

Daptomycin has also demonstrated in vitro activity against emerging multidrug-resistant gram-positive pathogens, including VISA (MIC, 8–16 µg/mL) and VRSA (MIC, ≥32 µg/mL). Howe et al[75] studied the in vitro activity of daptomycin against 6 strains of VISA collected worldwide (5 from the United States and 1 from Japan). All strains tested were susceptible to daptomycin, with MICs ranging from 0.5 to 1 µg/mL. The strain of VRSA (strain HMC3; MIC, ≥32 µg/mL) isolated at the Hershey Medical Center (Hershey, Pennsylvania) from a heel wound in a 70-year-old male patient was reported to be susceptible to daptomycin with an MIC of 0.5 µg/mL.[76]

The in vitro activity of daptomycin against selected gram-positive pathogens is summarized in **Table III**[64,67,69–71,73–76] and **Table IV**.[70–74,77] Studies have indicated that the MICs of daptomycin are not greatly affected by the resistance patterns of susceptible pathogens (MIC within 1 doubling dilution). This may be due to the unique mechanism of action of daptomycin that targets the bacterial membrane. Daptomycin may have an important role in the treatment of infections caused by multidrug-resistant pathogens. However, in our opinion, the in vitro activity of any antimicrobial agent does not necessarily translate into clinical usefulness, because the activity of a drug is also influenced by other factors such as the degree of in vivo protein binding, the ability to reach a therapeutic concentration at the infection site, and inoculum effects.

PHARMACODYNAMICS

Various time-kill studies have demonstrated that daptomycin exhibits rapid concentration-dependent in vitro

Table III. In vitro activity of daptomycin against selected staphylococci and enterococci.

Organism	Total No. of Clinical Isolates	MIC (µg/mL)	
		MIC_{90}	MIC Range
Staphylococcus aureus			
Oxacillin susceptible[67,69–71,73]	2332	0.25–0.5	0.015–1.0
Oxacillin resistant[67,69–71,73]	1054	0.5	0.12–2.0
Vancomycin intermediate[75]	6	0.5–1	–
Vancomycin resistant[76]	1	0.5	–
Coagulase-negative staphylococci[64,70,73,74]			
Oxacillin susceptible	765	0.25–0.5	0.03–2.0
Oxacillin resistant	984	0.25–1.0	0.004–2.0
Enterococcus faecalis[67,70,71,73]			
Vancomycin susceptible	4684	2.0	0.015–4.0
Vancomycin resistant	128	2.0–4.0	0.015–4.0
Enterococcus faecium[67,70,71,73]			
Vancomycin susceptible	730	2.0–4.0	0.015–8.0
Vancomycin resistant	689	2.0–4.0	0.03–8.0

MIC = minimum inhibitory concentration; MIC_{90} = minimum concentration to inhibit 90% growth; oxacillin susceptible = MIC, ≤2 µg/mL; oxacillin resistant = MIC, ≥4 µg/mL; vancomycin intermediate = MIC, 8–16 µg/mL; vancomycin resistant = MIC, ≥32 µg/mL; vancomycin susceptible = MIC, ≤4 µg/mL.

Table IV. In vitro activity of daptomycin against *Streptococcus pneumoniae* and selected *Streptococcus* species.

Organism	Total No. of Clinical Isolates	MIC (μg/mL)	
		MIC_{90}	MIC Range
Streptococcus pneumoniae[70,71,73]			
Penicillin susceptible	1720	0.12–0.25	0.015–1.0
Penicillin intermediate	505	0.25	0.015–0.5
Penicillin resistant	378	0.12–0.25	0.015–1.0
Streptococcus agalactiae[70,71,73]	848	0.25	0.03–1
Streptococcus pyogenes[71,73]	723	0.06	0.015–0.5
Viridans group streptococci[72,73]	518	0.5–1.0	0.12–2.0
Beta-hemolytic streptococci (group not specified)[72,74]	279	0.25–0.5	0.03–0.5
Group C streptococci[77]	42	0.5	0.06–0.5
Group G streptococci[77]	82	0.5	0.06–0.12

MIC = minimum inhibitory concentration; MIC_{90} = minimum concentration to inhibit 90% growth; penicillin susceptible = MIC, <0.06 μg/mL; penicillin intermediate = MIC, 0.12–1 μg/mL; penicillin resistant = MIC, >2 μg/mL.

bactericidal activity against staphylococci and enterococci, including resistant strains such as oxacillin-resistant *S epidermidis*, ORSA, VISA, VRSA, and VREF, with a 99.9% reduction in bacterial colony counts at 6 to 8 hours for all pathogens tested.[68,75,76,78–81]

Very few studies elucidating the effect of bacterial inoculum concentrations on daptomycin have been published. When tested against *Staphylococcus* and *Enterococcus* species at concentrations of 10^7 and 10^9 colony-forming units/mL, the MICs for both concentrations were the same.[82] Daptomycin appeared to have little or no inoculum effects. Daptomycin is >90% protein-bound, primarily to albumin.[24,44] In an in vitro pharmacokinetic model in which the bactericidal activity of daptomycin was tested against VREF, the mean time required for 99.9% killing was increased from 2.8 hours to 7 hours in the presence of a physiologic concentration of albumin (3.8–4.2 g/dL) in the test medium.[83] Jain et al[84] studied the bactericidal activity of daptomycin against LRVREF/VREF and reported a 16-fold increase in MIC when the test medium was supplemented with albumin at a concentration of 4 g/dL. Clinical failures with daptomycin in earlier studies, in which subjects were administered daptomycin 2 mg/kg daily (50% of the current FDA-approved dosage for complicated skin and skin-structure infections) for the treatment of bacteremia and endocarditis, could be explained partly by a low level of free active drug.[46,57] The clinical relevance of protein binding in daptomycin therapy remains to be delineated.

Daptomycin possesses a postantibiotic effect (ie, the length of time that bacterial growth is suppressed after brief exposure to an antibiotic) against gram-positive bacteria including *S aureus* (2.0–6.3 hours),[85] coagulase-negative staphylococci (1.1–2.4 hours),[85] *S pneumoniae* (1.0–2.5 hours),[85] and *E faecalis* (0.6–6.7 hours).[86]

Safdar et al[48] studied the in vivo pharmacodynamic activity of daptomycin in a neutropenic murine thigh infection model. Consistent with the concentration-dependent bactericidal activity of daptomycin, both the 24-hour AUC/MIC ratio (AUC_{0-24}/MIC) and the peak concentration/MIC ratio (peak/MIC) were strong predictors of in vivo efficacy (R^2 = 0.86, and 0.83, respectively). Efficacy was not related to the period of time when the serum concentration of daptomycin was above the MIC (R^2 = 0.47–0.50).[48] However, findings of other pharmacodynamics studies[47,87] suggested that the AUC/MIC ratio was a better pharmacodynamic parameter (R^2 = 0.939–0.990)[87] than the peak/MIC ratio for predicting the antibacterial efficacy of daptomycin.

Several investigators assessed the in vitro activity of daptomycin combined with ampicillin, aztreonam,

cefepime, ceftriaxone, fosfomycin, gentamicin, imipenem, oxacillin, rifampin, or tobramycin against multiple strains of *S aureus,* coagulase-negative staphylococci, *E faecalis,* and enterococci.[83,88–93] Overall, interactions of daptomycin with the antimicrobial agents were synergistic, additive, or indifferent. No antagonism was observed.[82,88–92,94] Therefore, daptomycin may be combined with other antibiotics in the treatment of infections due to gram-positive pathogens, although further studies are needed to confirm the in vivo efficacy of the combinations.

Development of spontaneous resistance to daptomycin is rare, with resistance rates of $<10^{-10}$ for *S aureus* and $<10^{-9}$ for *S epidermidis, E faecalis, E faecium,* and *S pneumoniae.*[93] Serial passages (N = 20) of a susceptible strain of *S aureus* (strain Sa42) through drug-gradient plates resulted in a mutant strain with a 16-fold increase in MIC. Eleven resistant *S aureus* mutant strains with MICs 8- to 32-fold higher than the original isolates were obtained after chemical mutagenesis with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine. Of note, none of the mutant isolates exhibited cross-resistance to vancomycin or ampicillin.[93] Emergence of resistance was noted on 2 occasions in Phase II/III clinical trials involving an *S aureus* strain (MIC 5 mg/mL[95]) from a patient with endocarditis, and an *E faecalis* strain (MIC 8 mg/mL[66]) from a patient with an infected decubitus ulcer. The mechanism of spontaneous resistance to daptomycin may be multifactorial and remains to be elucidated. To date, no reports of cross-resistance between daptomycin and other antimicrobial agents have been published.[66]

ANIMAL STUDIES

Daptomycin efficacy has been studied in rats,[54,88,96–102] rabbits,[103–106] hamsters,[107–109] and mice[110–112] in a variety of infection models. Although the majority of preclinical and animal studies were conducted in an endocarditis model,[49,96–98,103,104] efficacy has also been examined in animal models of pneumonia,[107,108] bacteremia,[110,111] osteomyelitis,[99,105] intra-abdominal infections,[109,112] skin and skin-structure infections,[54,100,101] and pyelonephritis.[88,102] Use of daptomycin in the prevention of aminoglycoside-induced nephropathy has also been examined in animal models.[113–116] Relative efficacy of daptomycin and comparator regimens in animal studies are summarized in **Table V**.[49,54,88,96–112] For details regarding experimental methods and statistical analyses, original citations should be reviewed. All statistically significant results were reported at $\alpha \leq 0.05$.

For the treatment of endocarditis, mixed results have been found: daptomycin appeared more effective than saline or no treatment or use of some antibiotic regimens[49,96,97,103,104] but not others.[98,106] Similarly, in the treatment of pneumonia, daptomycin was found to yield no better survival rates than saline treatment in some strains[107,108] but exhibited inferior activity compared with vancomycin in 1 study.[108] Despite dose-dependent bactericidal activity noted in the treatment of pathogens in 1 study of daptomycin use in bacteremia,[111] daptomycin did not significantly increase survival rate or sterilization of organ cultures when compared with controls or vancomycin at all doses in mice.[111] Limited success was also noted in the eradication of osteomyelitis with daptomycin or vancomycin,[99,105] although either treatment regimen may produce better results than no treatment among controls.[105] Of note, daptomycin was not detected in noninfected bone and reached a concentration of ~0.5 µg/mL in infected bone ($P < 0.05$). At this concentration (numerically lower than serum concentration), it was hypothesized that higher ionized calcium levels at the site of infection may have activated daptomycin in the treatment of osteomyelitis. In the treatment of intra-abdominal infections, daptomycin appears to prolong survival after onset of *Clostridium difficile* pseudomembranous colitis when compared with no treatment in hamsters.[109] However, prolongation occurs to the same duration as treatment with vancomycin in hamsters.[54,109] In animal studies of skin and skin-structure infections, daptomycin was more effective than untreated controls,[54] oxacillin,[100] and vancomycin.[100,101] Daptomycin may also be useful in the treatment of ventriculitis when administered as a single intraventricular dose.[106] In the treatment of pyelonephritis, daptomycin was more efficacious than vancomycin after several days of treatment and showed greater efficacy in a BID regimen than a QD regimen in 1 study[88] regardless of the addition of gentamicin. However, ampicillin plus gentamicin appeared to lower bacterial counts more than daptomycin-based regimens and additionally sterilized kidneys.[88]

Studies have also suggested that daptomycin may play a role in the prevention of aminoglycoside-

Table V. Summary of statistically significant differences between daptomycin and comparator treatment regimens in animal studies.

Daptomycin Regimen	Comparator Regimens	Primary Treatment End Points
Endocarditis		Reduction in bacterial count in cardiac vegetations
MSSA-infected rabbits		
Daptomycin 8 mg/kg TID[97]	Teicoplanin 12.5 mg/kg BID	$P < 0.005$
	Teicoplanin 40 mg/kg BID	P = NS
	Vancomycin 17.5 mg/kg QID	P = NS
	Untreated controls	$P < 0.001$
MSSA-infected rats		
Daptomcyin 10 mg/kg BID[98]	Vancomycin 30 mg/kg QID	$P < 0.001$
	Vancomycin 30 mg/kg BID	P = NS
	Cloxacillin 200 mg/kg q 5 h	P = NS
	Controls	P = NS
MRSA-infected rabbits		
Daptomycin 8 mg/kg TID[97]	Teicoplanin 12.5 mg/kg BID	P = NS
	Teicoplanin 40 mg/kg BID	P = NS
	Vancomycin 17.5 mg/kg QID	P = NS
	Untreated control	$P < 0.001$
E faecalis–infected rabbits		
Daptomycin 10 mg/kg BID[103]	Penicillin G procaine 1.2×10^6 units BID	$P < 0.001$*
	Vancomycin 75 mg/kg BID	$P < 0.001$
	Vancomycin 75 mg/kg + gentamicin 5 mg/kg BID	$P < 0.001$*
	Daptomycin 10 mg/kg + gentamicin 5 mg/kg BID	$P < 0.001$*
	Untreated controls	$P < 0.001$
Daptomycin 10 mg/kg BID + gentamicin 5 mg/kg BID[103]	Vancomycin 75 mg/kg + gentamicin 5 mg/kg BID	$P < 0.001$*
	Penicillin G procaine 1.2×10^6 units + gentamicin 5 mg/kg BID	$P = 0.39$
E faecalis–infected rats		
Daptomycin 25 or 50 mg/kg TID[96]	Vancomycin 100 mg/kg QD	$P < 0.05$
	Imipenem 300 mg/kg QD	P = NS
	Gentamicin 30 mg/kg QD	P = NS
	Ampicillin 400/sulbactam 100 mg/kg QD	$P < 0.05$
	Untreated controls	$P < 0.001$
E faecium–infected rabbits		
Daptomycin 20 mg/kg BID[104]	Vancomycin 20 mg/kg BID	$P < 0.01$
	Ampicillin 100 mg/kg TID	$P < 0.01$
	Ampicillin 100 mg/kg TID + gentamicin 2.5 mg/kg BID	$P < 0.01$
	Controls	$P < 0.01$
Daptomycin 10 mg/kg BID[49]	Daptomycin 10 mg/kg BID	P = NS
	Teicoplanin 10 mg/kg BID	$P < 0.05$
	Teicoplanin 40 mg/kg BID	$P < 0.01$
	Gentamicin 6 mg/kg BID	P = NS
	Daptomycin 10 mg/kg BID + gentamicin 6 mg/kg BID	P = NS
	Daptomycin 12 mg/kg TID + gentamicin 6 mg BID	$P < 0.01$
	Teicoplanin 10 mg/kg BID + gentamicin 6 mg/kg BID	P = NS
	Teicoplanin 40 mg/kg BID + gentamicin 6 mg/kg BID	P = NS
	Controls	$P < 0.05$

(continued)

Table V. (Continued)

Daptomycin Regimen	Comparator Regimens	Primary Treatment End Points
Pneumonia		
MRSA-infected hamsters	Vancomycin 40 mg/kg QD	Mean bacterial count/bacterial killing rate: P = NS for both comparator groups
Daptomycin 20 mg/kg QD[107]	Controls	
Daptomycin 10 mg/kg BID[108]	Vancomycin 15 mg/kg BID	Survival rate: $P < 0.002$*
	Saline-treated controls	Survival rate: NS
Bacteremia		
S aureus–infected mice	Vancomycin 10 mg/kg BID	Survival rate/sterilization of cultures: P = NS
Daptomycin 5 or 10 mg/kg BID[111]	Vancomycin 5 mg/kg BID	$P = 0.04$
Gram-positive infected mice	Vancomycin 1–50 mg/kg × 1 dose	Reduction in bacterial count: Treatment results not compared
Daptomycin 1–50 mg/kg × 1 dose[110]	Ceftriaxone 1–50 mg/kg × 1 dose	
Osteomyelitis		Reduction in bacterial count
MRSA-infected rabbits		
Daptomycin 4 mg/kg BID[105]	Vancomycin 40 mg/kg QID	P = NS
	Untreated controls	$P < 0.001$
MSSA-infected rabbits		
Daptomycin 10 mg/kg BID[99]	Vancomycin 80 mg/kg BID	$P = 0.023$*
	Control	P = NS
Intra-abdominal infections		Survival time/colonization
C difficile–infected hamsters		
Daptomycin 0.05 mg QD[109]	Vancomycin 5 mg QD	Prolongation of survival time: P = NS
Streptomycin-treated, *E faecalis*–infected mice		
Daptomycin 10 mg/kg BID[112]	Untreated controls	Incidence of colonization: $P < 0.004$ for various organs
Skin and skin-structure infections		Reduction in bacterial count
MSSA-infected rats		
Daptomycin 30 mg/kg BID[100]	Oxacillin 200 mg/kg BID	$P < 0.01$
	Vancomycin 50 mg/kg BID	$P < 0.01$
	Untreated controls	$P < 0.01$
MRSA-infected rats		
Daptomycin 10 mg/kg BID[101]	Vancomycin 125 mg/kg BID	$P < 0.003$
	Controls administered water	$P < 0.05$
Daptomycin 10 mg/kg BID[103]	Vancomycin 125 mg/kg BID	$P < 0.003$
	Controls administered water	$P < 0.05$
Daptomycin 30 mg/kg QD[54]	Vancomycin 50 mg/kg BID	P = NS
	Untreated controls	$P = 0.001$
Ventriculitis		Reduction in bacterial count
S aureus–infected rabbits[106]		
Daptomycin 7.5 μg × 1 dose	Vancomycin 30 or 120 μg × 1 dose	P = ND
	Untreated controls	$P < 0.01$

(continued)

Table V. (Continued)

Daptomycin Regimen	Comparator Regimens	Primary Treatment End Points
Pyelonephritis		Reduction in bacterial count
E faecalis–infected rats		
Daptomycin 10 mg/kg BID[88]	Daptomycin 20 mg/kg QD	$P < 0.01$
	Daptomycin 10 mg/kg BID + gentamicin 1.5 mg/kg BID	NS
	Vancomycin 20 mg/kg BID	$P < 0.005$
	Vancomycin 20 mg/kg BID + gentamicin 1.5 mg/kg BID	NS
	Ampicillin 30 mg TID	NS
	Ampicillin 30 mg BID + gentamicin 1.5 mg/kg BID	$P < 0.001$*
	Untreated controls	$P < 0.01$
Daptomycin 10 mg/kg BID[102]	Gentamicin 0.8 mg BID	NS
	Daptomycin 10 mg/kg BID + gentamicin 0.8 mg BID	Level of statistical significance not reported
	Untreated controls	P = NS

MSSA = methicillin-sensitive *Staphylococcus aureus*; MRSA= methicillin-resistant *S aureus*; *E faecalis* = *Enterococcus faecalis*; *E faecium* = *Enterococcus faecium*; *C difficile* = *Clostridium difficile*; ND = data not reported.
*Comparator regimen more effective than daptomycin regimen.

induced nephrotoxicity by interfering with the interaction between aminoglycosides and phosphatidylinositol receptors in cell membranes. Without daptomycin, pinocytosis of aminoglycosides into cytoplasmic vacuoles and fusion of these vacuoles with lysosomes results in the formation of myeloid bodies and the bursting of lysosomes, followed by tubular cell necrosis and impaired renal function.[114,115] However, different patterns of accumulation of daptomycin in myeloid bodies of lysosomes when administered with or without tobramycin[116] support the speculated mechanism of daptomycin interference with aminoglycoside binding in membranes of renal proximal tubular cells.[113–115]

CLINICAL STUDIES

Unfortunately, to date, there have been few published studies describing the efficacy of daptomycin in the treatment of infections in human subjects. Several small-scale Phase II studies were initiated by Eli Lilly and Company in open-label trials during the years 1987 to 1990, including B8B-EW-AVAH (6 mg/kg loading dose followed by 3 mg/kg BID) and B8B-MC-AVAE/B8B-EW-AVAG (daptomycin 2 mg/kg QD) for the treatment of complicated skin and skin-structure infections or B8B-MC-AVAM (loading dose 6 mg/kg followed by 3 mg/kg BID) for the treatment of comorbid bacteremia and endocarditis.[117] However, these studies were terminated early due to adverse events (AEs) or slow enrollment.[117] The majority of information discussed in this section is only available in abstract or poster form or from documentation submitted to the FDA for drug approval.[117] Based on evaluation of safety data in earlier preclinical and clinical studies, Cubist Pharmaceuticals, Inc., modified the recommended administration schedule from daptomycin in divided daily doses to a QD dose regimen.[2,3]

Complicated Skin and Skin-Structure Infections

Results from 2 multicenter, multinational, investigator-blinded, randomized Phase III studies of skin and skin-structure infections, conducted in adults aged 18 to 85 years between March 2000 and December 2000, were combined and reported by Arbeit at al.[118] Data for study DAP-SST-9801 were collected from 64 sites in the United States and 5 in South Africa; data from DAP-SST-9901 were collected from 42 sites in Europe, 20 in South Africa, 5 in Australia, and 3 in Israel. The same study design was used in both studies. Patients were included if they had a complicated skin or skin-structure infection caused by a known or suspected gram-positive bacterial pathogen and required hospitalization with IV antibiotics for ≥96 hours. Types of infections included major abscesses, infected ulcers, and wound infections.[117] Patients were excluded if they had superficial skin

infections, multiple infected ulcers at different sites, gangrene, perirectal abscesses, or third-degree burns; required curative surgery or had bacteremia at or before study entry; had a life expectancy <2 months; or had infections due primarily to gram-negative pathogens or pathogens showing resistance to daptomycin or vancomycin.

The purpose of these studies[118] was to compare the efficacy of daptomycin 4 mg/kg IV QD versus comparator regimens consisting of penicillinase-resistant penicillins (ie, cloxacillin, nafcillin, oxacillin, or flucloxacillin 4–12 g/d IV in equally divided doses) or vancomycin 1 g IV QD. Patients recruited in the studies were first randomly assigned to a comparator group (either penicillinase-resistant penicillins or vancomycin). They were then randomized to receive 7 to 14 days of daptomycin or comparator treatment (according to the earlier assignment). Change to oral antibiotics was allowed after patients received at least 3 days of IV antibiotics, showed clinical improvement (as evaluated by an investigator blind to treatment assignment), were found to have infections with pathogens susceptible to oral antibiotics, or had a compelling reason to stop IV antibiotics (eg, discharge from hospital).

The primary end point for the study[118] was test-of-cure evaluation conducted 6 to 20 days after the last dose of antibiotic. The site of infection was inspected by investigators blind to treatment assignment. The goal of the study was to demonstrate *noninferiority* (defined as the upper limit of the 95% CI of <10% difference) between daptomycin and comparator treatment (ie, comparator success rate minus daptomycin success rate). *Clinical success* was defined as resolution of signs and symptoms of infection sufficient to discontinue antibiotic therapy. Patients were also evaluated for clinical relapse or recurrence at 20 to 28 days after completion of treatment. Inadequate response to treatment during the follow-up period was classified as *clinical failure*. Statistical comparisons, summarized here, were conducted for the intent-to-treat (ITT) group, which included patients who received ≥1 dose of study medication, and the clinically evaluable group, which consisted of patients in the ITT group who met inclusion and exclusion criteria for recruitment and did not present with confounding factors (eg, use of antibiotics for intercurrent infections).

Overall, 1092 patients were included in the ITT analysis and 902 patients in the clinically evaluable population for efficacy and safety analyses.[118] No differences in baseline characteristics between the daptomycin and comparator groups (n = 534 and n = 558, respectively) were found for age, race, sex, comorbid conditions (ie, diabetes mellitus, peripheral vascular disease, immunocompromised status), or baseline diagnosis. Approximately 88% of patients in each group completed therapy; therapeutic failure was cited as the most common reason for discontinuation of therapy. Sixty percent (337/558) of comparator-treated patients received penicillinase-resistant penicillins. In addition, aztreonam and/or metronidazole were administered to 127 patients in the daptomycin-treated group and 148 patients in the comparator-treated group. No significant differences in clinical success rates were seen between daptomycin or comparator groups in the ITT group (71.5% vs 71.1%; 95% CI, –5.8 to 5.0; P = NS) or the clinically evaluable group (83.4% vs 84.2%; 95% CI, –4.0 to 5.6; P = NS). In the ITT group, 10.2% of patients switched from IV to oral therapy, although the choice of step-down therapy was not detailed. Among patients who received IV antibiotics only, 63% of daptomycin-treated patients received 4 to 7 days of therapy compared with 33% of patients in the comparator group (P < 0.001), suggesting a shorter duration of IV treatment may yield similar treatment efficacy. In addition, no difference in rates of clinical relapse or recurrence were detected between the daptomycin (4% [15/355]) and comparator (5% [20/367]) treatment groups (95% CI, –4.4% to 1.9%).

In the safety analyses,[118] AEs were classified as mild, moderate, or marked (*severe*) according to the World Health Organization Toxicity Grading Scale. Fifteen patients in the daptomycin group (3%) and 17 patients in the comparator group (3%) discontinued treatment due to AEs. Although the majority of AEs were not related to the study medications, 18% of daptomycin-treated patients (94/534) and 21% of comparator-treated patients (119/558) experienced treatment-related AEs. AEs reported in ≥5% of patients were as follows: for daptomycin, constipation (6%), nausea (6%), injection-site reactions (6%), headache (5%), and diarrhea (5%); for vancomycin, nausea (10%), constipation (7%), and injection-site reactions (8%); and for semisynthetic penicillins,

headache (5%) and injection-site reactions (6%). At least 1 severe AE was seen in 11% of daptomycin-treated and 9% of comparator-treated patients. Overall, daptomycin was comparable to conventional agents for gram-positive skin and skin-structure infections in terms of clinical efficacy and safety.

For the DAP-SST-9901 trial, an interim analysis of patients with dual infection with *S aureus* and hemolytic streptococci in complicated skin and soft tissue infections was reported in abstract form by Roditi et al.[119] Among the 562 patients recruited (until the time of publication of the abstract), 468 had infection with ≥1 gram-positive pathogen. For example, infection with *S aureus* alone was found in 209 patients, whereas dual infection with hemolytic streptococci was found in 97 patients, other streptococci in 5 patients, enterococci in 10 patients, and 1 patient with anaerobic infection. Infection with hemolytic streptococci alone was found in 75 patients and dual infection with enterococci in 3 patients. Other types of dual infection included 2 patients with 2 nonhemolytic streptococcal strains, 6 with nonhemolytic streptococci and enterococci, 1 with nonhemolytic streptococci and anaerobe infection, and 2 patients with 2 enterococcal strains. Treatment regimens consisted of daptomycin or standard therapy with semisynthetic penicillin or vancomycin. Aztreonam or metronidazole could be added, although details of these antimicrobial treatments were not included in the abstract. Overall success rates for dual infection with *S aureus* and hemolytic streptococci were lower than with other dual infections (73.2% vs 86.5%; $P = 0.004$, Fisher exact test). Regardless of dual infection status, Kaplan-Meier analyses also found that *S aureus* infection persisted longer in patients with diabetes mellitus than in those without it (75% showing clearance at 15 vs 31 days; $P = 0.01$), with no differences in rate of clearance between daptomycin and standard treatment groups (20 vs 33 days, respectively; $P = 0.17$). From this report, few conclusions regarding the efficacy of daptomycin or standard therapy could be made in this subset of patients.[119]

In a separate abstract describing the resolution of clinical signs for the same subset of patients,[120] patients were evaluated for the severity of 8 clinical signs of skin and soft tissue infections (including tenderness, induration, and purulence). Each sign was assigned a score of 0 for none present, 1 for mild, 2 for moderate, or 3 for severe; a composite score was then determined for each patient. In the ITT analysis, both the daptomycin and comparator groups showed 81% clinical efficacy. At baseline, both groups had a median score of 13. After 3 to 4 days of treatment, daptomycin recipients showed a median decrease in scores of 5, whereas the comparator group showed a decrease of 4 ($P < 0.05$). Median duration of treatment with daptomycin was also shorter (7 vs 8 days; $P < 0.05$), suggesting similar efficacy may be achieved more rapidly.[120]

Bacteremia

Two ongoing Phase II, open-label clinical trials evaluating the efficacy and safety of daptomycin 4 mg/kg QD, 6 mg/kg QD, or 3 mg/kg BID for treatment of bacteremia are under way, as reported in an abstract by Snydman.[121] As of the year 2000, 86% of patients treated with daptomycin 4 mg/kg QD showed clinical response (although not defined in the abstract), compared with 69% of patients treated with vancomycin 1 g BID. No differences in AE profiles were found between the 2 groups. No details regarding the number of participants or specific details about types of AEs were reported at the time of publication of the abstract. Instead, study details provided in records submitted to the FDA[117] showed that in the DAP-BAC-9803 study, 24 patients received daptomycin 4 mg/kg QD, 26 patients received daptomycin 6 mg/kg QD, and 24 patients received daptomycin 3 mg/kg BID after a loading dose of 6 mg/kg. The comparator group consisted of 24 patients who received standard therapy with vancomycin 1 g BID or nafcillin or oxacillin 4 to 12 g daily in equally divided doses. All patients had confirmed or presumed gram-positive bacteremia.

In the DAP-RRC-9804 study,[117] daptomycin was administered in an open-label, noncomparator, multicenter trial using 3 dosing regimens for bacteremia: 4 mg/kg QD, 6 mg/kg QD, or 3 mg/kg BID after a 6-mg/kg loading dose. Patients with other indications for treatment of gram-positive infections were also included in this study: complicated skin and skin-structure infections (4 mg/kg QD), lower respiratory tract infections (6 mg/kg QD), intra-abdominal infections (6 mg/kg QD), and complicated urinary tract infections due to vancomycin-resistant or otherwise refractory-to-treatment pathogens (4 mg/kg QD). Al-

though all patients received treatment for ≥14 days, this trial was terminated early due to slow enrollment.[117]

Two cases of bacteremia in patients undergoing neutropenic bone marrow transplantation were treated with daptomycin after inadequate treatment with vancomycin.[122] In the first case, an 18-year-old woman with recurrent Hodgkin's lymphoma developed bacteremia after chemotherapy and transplantation, despite prophylactic regimens with ciprofloxacin, sulfamethoxazole-trimethoprim, and acyclovir. Imipenem and vancomycin were started, but imipenem was changed to cefepime in response to rash and amphotericin was added to the regimen. The patient developed grade 2 graft-versus-host disease, which was treated with hydrocortisone, and subsequently septic shock with a blood culture positive for *Leuconostoc mesenteroides* resistant to vancomycin (MIC > 4 μg/mL). Because the isolate was sensitive to daptomycin (MIC < 0.03 μg/mL), daptomycin was initiated with a 400-mg bolus followed by 4.5 mg/kg q 36 h (adjusted for CrCl 55 mL/min) for 8 days and then increased to 6 mg/kg QD after improvement in renal function for a total of 15 days of treatment. The patient was discharged on day 42 with no side effects to daptomycin reported.

The second case also involved *L mesenteroides*.[122] A 35-year-old man with a relapse of acute myeloblastic leukemia complicated by a line-related bacteremia, penicillin-induced rash, peripheral neuropathy, and renal insufficiency had to wait 3 months until allogenic bone marrow transplantation. Eight days after relapse, the patient was found to have bacteremia with *L mesenteroides* susceptible to daptomycin. Treatment was started at 6 mg/kg QD and continued until a lumbar puncture 3 days later revealed the presence of leukemic meningitis with *S epidermidis* in cerebrospinal fluid. Daptomycin was discontinued and vancomycin was started until the bacteremia resumed and daptomycin had to be continued for 3 more weeks. One month after resolution of the infection, the patient died of complications related to leukemia. For the treatment of catheter-related bacteremia due to a vancomycin-resistant nosocomial pathogen, overall daptomycin was safe and effective.

Pneumonia

Use of daptomycin was investigated for the treatment of moderate to severe community-acquired pneumonia (CAP) due to *S pneumoniae* in the studies DAP-CAP-00-05 and DAP-CAP-00-08.[117] Both were Phase II, randomized, multicenter, multinational, double-blind, parallel-treated, active-controlled trials comparing the efficacy and safety of daptomycin 4 mg/kg QD versus ceftriaxone 2 g QD in the comparator arm. Aztreonam could be added for gram-negative coverage, according to the study investigators. Anticipated treatment duration was 5 to 14 days with test-of-cure assessed at 7 to 14 days after the last dose of study medication. Men and women aged ≥18 years with pneumonia caused by known or suspected gram-positive bacteria and requiring hospitalization for IV antibiotics for ≥5 days were considered for the trials. In the DAP-CAP-00-05 study, which was conducted at centers in the United States, Europe, Canada, Australia, South America, and New Zealand, 355 patients were randomized to the daptomycin group and 359 patients to the comparator group. However, daptomycin treatment failed to meet the predetermined criterion for noninferiority (<10% difference in clinical success between daptomycin and ceftriaxone at the upper 95% CI for clinical success). Based on the results of this study, DAP-CAP-00-08 was terminated with 100 patients receiving daptomycin and 101 patients receiving ceftriaxone. Among all patients who received study medications in these 2 studies, 58.2% (265/455) in the daptomycin group and 60.7% (279/460) in the ceftriaxone group received medications for 7 to 14 days. Overall, more patients receiving daptomycin treatment prematurely discontinued treatment (23.3% [106/455] vs 14.1% [65/460]), with more patients in this group citing clinical failure as the reason for discontinuation of therapy (9.7% [44/455] vs 5.0% [23/460], respectively). Thus, daptomycin is not indicated for the treatment of pneumonia, as specifically noted in the package insert.[24] Limited penetration and accumulation of daptomycin at alveolar sites of infection may contribute to its lack of clinical efficacy in the treatment of pneumonia.

Complicated Urinary Tract Infections

In addition to study DAP-RRC-9804,[117] which included patients with complicated urinary tract infections, study DAP-00-03 was planned as an open-label, Phase III comparison of daptomycin 4 mg/kg QD versus ciprofloxacin 400 mg.[117] Each arm of the

study recruited 34 patients, and the majority of these patients received treatment for 2 to 14 days. However, the study was terminated early due to slow enrollment.

Endocarditis

An early study of *S aureus* endocarditis—B8B-MC-AVAM—compared the efficacy and safety of daptomycin 3 mg/kg BID versus comparator treatment (eg, nafcillin, gentamicin).[117] During the study, 14.6% (13/89) of patients in the daptomycin group and 17.1% (6/35) in the comparator group died. Causes of death were not attributed to the medications administered (eg, abscess, cardiac arrest, multiorgan failure, respiratory failure, gastric aspiration). However, it was hypothesized that despite adequate treatment of staphylococcal bacteremia with daptomycin (3 mg/kg BID), this dose may not be effective in the treatment of endocarditis due to this pathogen. Subsequently, the study DAP-IE-01-02 was proposed using daptomycin 6 mg/kg QD. Due to concerns regarding subtherapeutic response and potential consequences, the study investigators sought (and received) FDA approval to recruit only patients with right-sided endocarditis.[117] No results of this study were available at the time of manuscript preparation.

SAFETY PROFILE

Safety data submitted to the FDA for approval of daptomycin consisted of data from use of this agent in 602 participants in Phase I studies, 349 in Phase II studies, and 989 in Phase III studies.[117] This section of the present article reviews safety data from preclinical and clinical studies and subsequent recommendations for the dosing of daptomycin. In addition, it discusses the occurrence of daptomycin-related serious AEs and the need for discontinuation of daptomycin during clinical studies, with an emphasis on results from Phase III trials supporting the use of daptomycin for the FDA-approved indication of treatment of complicated skin and skin-structure infections.

Toxicology reports on file with Lilly Research Laboratories (Indianapolis, Indiana) have been summarized by Oleson et al.[123] Of particular concern was the emergence of skeletal muscle toxicity in early animal and human studies.[117,123] Results of pharmacokinetic studies in dogs comparing daptomycin 75 mg/kg in 1 single daily dose or divided into 3 daily doses[123] suggested that muscle toxicity may be related to the dose interval rather than the C_{max} or extent of accumulation. Daptomycin 75 mg/kg QD yielded a 3.3-fold higher mean (SD) C_{max} than the same total daily dose administered TID (540 [112] µg/mL vs 238 [22] µg/mL). In comparison, 25 mg/kg QD yielded a mean (SD) C_{max} of 165 (44) µg/mL. For AUC_{0-24}, there was a proportionate increase in mean (SD) AUC at the same dose interval (682 [44] µg·h/mL for 25 mg/kg QD vs 1840 [374] µg·h/mL for 75 mg/kg QD), compared with slightly greater accumulation (1.37-fold) with the fractionated regimen (mean [SD], 2526 [197] µg·h/mL for 25 mg/kg TID). However, despite a higher C_{max} with 75 mg/kg QD, daptomycin 25 mg/kg TID yielded a nearly 4-fold greater increase in mean [SD] creatine phosphokinase (CPK) after 8 days of treatment (3996 [315] U/L vs 991 [421] U/L). Measurement of trough concentration showed a minimal concentration of 27 µg/mL for the fractionated regimen at the end of the 8-hour dose interval. For the 75-mg/kg QD regimen, the concentration was already below this trough at 12 hours after administration.

With microscopy, minimal degeneration and regeneration of myofibers was observed with no evidence of necrosis, cell lysis, or fibrosis. No statistically significant difference in incidence of myofiber lesions was found between 75 mg/kg as a single daily dose or in 3 divided doses.[123] Instead, minimal, nonsuppurative inflammation secondary to skeletal muscle degeneration was seen. Based on the animal studies showing a higher risk of skeletal muscle toxicity with same total daily dose divided into smaller fractions than administered as a single daily dose despite no greater C_{max}, the investigators hypothesized that increased duration between doses of daptomycin may allow for repair of effects on skeletal muscle.[123] No progression of toxicity was detected with QD administration after 6 months. Lack of fibrosis (cell lysis) even after 20 days of treatment suggested daptomycin caused leakage of CPK from myofibers secondary to membrane perturbation. Daptomycin-induced myopathy appeared to be specific to skeletal muscle and also appeared to be nonprogressive and readily reversible in nature. Results from safety analyses in dogs have been extrapolated to humans, suggesting that daptomycin should be administered in a QD regimen to reduce the potential for skeletal muscle toxicity.[123]

In a Phase I dose-escalation trial,[118] 2 of 5 participants receiving daptomycin dosed at 4 mg/kg BID experienced acute increases in CPK >10 times the upper limit of normal (ie, peak CPK values >10,000 and 20,812 U/L for these participants) with muscle weakness and myalgia. Muscle effects were reversible after discontinuation of daptomycin. Three other subjects in clinical pharmacology studies also discontinued participation due to drug-related, asymptomatic elevation of CPK. Maximum values were 1940 or 1593 U/L after 14 or 7 days of daptomycin 6 mg/kg QD, respectively, and 4498 U/L after 5 doses of daptomycin (loading dose 4 mg/kg, followed by 3 mg/kg QD). Patients also presented with MM dimeric (muscle) isozyme pattern.[117] Elevations in CPK resolved within 2 weeks of discontinuation of daptomycin. In Phase II studies, 4 patients also discontinued daptomycin after increases in CPK occurred. Seven patients in Phase III studies for the treatment of CAP also showed AEs affecting the musculoskeletal or connective tissue systems. However, in a later pharmacokinetic study using daptomycin 8 mg/kg every 24 hours, transient increases in CPK to <2.5 times the upper limit of normal were observed in 2 participants for only 2 days and were not associated with muscle symptoms. One of these subjects continued to receive 8 mg/kg QD for 14 days without further increases in CPK.[45]

A preliminary evaluation of the incidence of skeletal muscle effects associated with daptomycin treatment (4 mg/kg QD for 7–14 days) among patients in the Phase III trials described by Arbeit et al[118] was presented in poster form by Knapp et al.[124] AEs and elevation in serum CPK were monitored throughout the study. Baseline levels of CPK >500 U/L were seen in 14.4% of patients (77/534) treated with daptomycin and 16.5% of patients (92/558) treated with semisynthetic penicillins or vancomycin (ie, comparator group). Approximately 70% of these elevations resolved with antimicrobial treatment, suggesting that the elevations were associated with infection. Transient elevations in CPK occurred in 3.4% (18/354) of daptomycin-treated and 3.6% (20/558) of comparator-treated patients, particularly in association with adjunctive surgery or intramuscular injection, and these resolved even with continued antimicrobial treatment. Signs and symptoms of skeletal muscle damage (eg, myalgia, weakness) were observed in 6.4% (34/534) and 5.0% (28/558), respectively. However, skeletal muscle effects were not associated with elevations in CPK and resolved with continued treatment. Only 1 patient (0.2%) in the daptomycin group appeared to show a rise in CPK accompanied by muscle pain and weakness that may be associated with the drug. After 10 days of daptomycin, CPK concentration peaked at 10,320 U/L. After discontinuation of the drug, CPK and muscle symptoms resolved. Thus, skeletal muscle toxicity did not appear to be a common side effect among patients receiving daptomycin 4 mg/kg QD for the treatment of complicated skin and skin-structure infections.

Despite changes associated with markers of skeletal muscle toxicity, Phase I studies suggest cardiac tissue does not appear to be a target of daptomycin-associated muscle toxicity.[117] In preclinical studies, in vitro concentrations of daptomycin 20- to 25-fold higher than the C_{max} expected with a dose of daptomycin 4 mg/kg QD did not affect cardiac muscle function. Exposure to daptomycin for 6 months showed no histopathologic conditions in cardiac muscle function in dogs. Moreover, 60 human subjects exposed to daptomycin 6 mg/kg QD for 14 days showed no cardiac changes on electrocardiogram. Thus, daptomycin-associated muscle toxicity did not appear to involve cardiac tissue.

In addition to discontinuation of study medications due to skeletal muscle toxicity, daptomycin use has also been associated with few cases of neuropathy in clinical studies.[117] One patient in study B8B-EW-AVAH showed a 50% reduction in nerve conduction velocity (NCV) amplitude after receiving a 1-mg dose of daptomycin. This study was halted after 4 of 50 intended participants had been recruited. In study B8B-MC-AVAM, 1 patient also discontinued daptomycin treatment secondary to neuropathy. Doses used in these 2 Phase II studies were daptomycin 6-mg/kg loading dose followed by 3 mg/kg BID. The second patient noticed tingling in 1 foot lasting 1 day on day 12 of treatment. Despite normal NCVs on day 4, repeat NCVs on day 18 showed moderate to severe neuropathy. Sensory sural nerve testing showed a lack of action potentials in distal and proximal sensory nerves, which was classified as probably related to study medication. Thus, the patient was withdrawn from the study. Another patient who received daptomycin 2 mg/kg QD for 5 days in study B8B-MC-AVAE/B8B-EW-AVAG for skin and skin-structure

infections also showed a 50% reduction in NCVs on day 10 compared with baseline measurements on day 2 of treatment. Unlike the previous case, this patient was asymptomatic. After discontinuation of study medications, neither patient returned for follow-up.

Although not resulting in discontinuation of study medications, neurologic changes classified as serious AEs were also seen in a select number of patients.[117] In Phase I and II studies, 4 patients developed Bell's palsy or other facial palsy while receiving daptomycin. Only 1 of these patients discontinued study medication. One additional patient also showed a reduction in NCV during 1 Phase II study. Two patients in Phase III studies also developed paresthesias. However, despite the fact that the occurrence of neuropathy, cranial neuropathy, and changes in NCV suggested daptomycin use may be associated with neuropathic or neurologic toxicity, no differences in the rate of occurrence were found between the daptomycin- and comparator-treated groups.

Other reasons to discontinue study medications included diarrhea, acute respiratory insufficiency leading to coma, severe respiratory failure, and elevation in cardiac enzymes in patients participating in Phase III trials for the treatment of CAP.[117] Only 1 patient required discontinuation of study medications for each of the events listed. Among serious AEs possibly or probably related to study medications in Phase II and III studies (yet not leading to discontinuation of daptomycin) were cholecystitis, leukopenia, pericardial effusion, complete atrioventricular block, acute renal failure, thrombocytopenia, hypersensitivity reaction, and eosinophilia, each occurring in 1 patient. Twenty-eight patients also experienced AEs of the gastrointestinal system.

No deaths during the Phase I, II, or III studies were attributed to daptomycin as a study medication. However, 1 patient receiving daptomycin for complicated urinary tract infection developed worsening atrial fibrillation and complete heart block. Despite a medical history of such arrhythmia, daptomycin use could not be excluded as a possible factor in the patient's death.[117]

The incidence of AEs that occurred in ≥2% of patients in the DAP-SST-9801 and DAP-SST-9901 studies are listed in **Table VI**.[24,118] There were no differences in the incidence of AEs between the treatment groups. Because early studies suggested that myopathy or muscle damage might have been a concern, CPK levels were measured at baseline, during treatment, and after completion of therapy. No significant differences were seen in CPK levels or in the incidence of CPK elevation among patients receiving daptomycin (2.1% [11/534]) or comparator treatment (1.4% [8/558]). Two patients in the daptomycin group discontinued treatment after 9 to 10 days of therapy with elevated CPK levels. Only 1 patient was symptomatic. As previously described,[118] muscle symptoms resolved after 72 hours and CPK elevations returned to within normal limits by the follow-up period of the study.

Pooled laboratory data from DAP-SST-9801 and DAP-SST-9901 showed no differences in hematologic parameters, blood chemistry, or hepatobiliary function between the 2 treatment groups.[117] Despite preclinical data in rats suggesting a dose-dependent, reversible elevation in markers of nephrotoxicity (eg, excretion of urinary tubular cells and malate dehydrogenase) and electron microscopy findings of partial loss of renal brush-border cells in the proximal tubule,[125] review of safety data from clinical studies has not confirmed that daptomycin use may be associated with renal toxicity.

Only 1 patient in the complicated skin and skin-structure infection studies showed an increase in total bilirubin >1.5 times the upper limit of normal.[117] The maximum alanine aminotransferase (ALT) level noted was 280 U/L and maximum aspartate aminotransferase (AST) was 386 U/L. Although hepatotoxicity and elevation in liver function test results were not characteristic AEs associated with daptomycin use in clinical trials, a 24-year-old HIV-positive female patient receiving daptomycin (3 mg/kg BID) for *S aureus* endocarditis experienced elevation in liver enzymes (to ALT 1374 U/L and AST 357 U/L) during the third week of treatment. Two weeks after discontinuation of daptomycin, enzyme levels began to decline and complete resolution was seen after 4 weeks.[117]

Overall, data on daptomycin safety at 4 mg/kg QD for up to 14 days of treatment showed no difference between daptomycin and comparative antimicrobial therapy.[117] Because skeletal muscle toxicity is the chief concern regarding the safety of daptomycin, patients should be monitored for symptoms of muscle pain or weakness, especially in distal extremities. The manufacturer also recommends that CPK levels be assessed

Table VI. Percentage incidence of adverse events occurring in ≥2% of patients in Phase III trials of complicated skin and skin-structure infections.[24,118]

Adverse Event	Daptomycin Group (n = 534)	Comparator Group* (n = 558)
Constipation	33 (6.2)	38 (6.8)
Injection-site reactions	31 (5.8)	43 (7.7)
Nausea	31 (5.8)	53 (9.5)
Headache	29 (5.4)	30 (5.4)
Diarrhea	28 (5.2)	24 (4.3)
Insomnia	24 (4.5)	30 (5.4)
Rash	23 (4.3)	21 (3.8)
Vomiting	17 (3.2)	21 (3.8)
Abnormal liver function test results	16 (3.0)	9 (1.6)
Elevated CPK	15 (2.8)	10 (1.8)
Pruritus	15 (2.8)	21 (3.8)
Fungal infections	14 (2.6)	18 (3.2)
Hypotension	13 (2.4)	8 (1.4)
Urinary tract infections	13 (2.4)	3 (0.5)
Dizziness	12 (2.2)	11 (2.0)
Renal failure	12 (2.2)	15 (2.7)
Anemia	11 (2.1)	13 (2.3)
Dyspnea	11 (2.1)	9 (1.6)
Fever	10 (1.9)	14 (2.5)
Limb pain	8 (1.5)	11 (2.0)
Hypertension	6 (1.1)	11 (2.0)
Arthralgia	5 (0.9)	12 (2.2)
Dyspepsia	5 (0.9)	14 (2.5)

CPK = creatine phosphokinase.
*Comparator group consisted of treatment with vancomycin or semisynthetic penicillins.

weekly with daptomycin use.[24] Although a small study (N = 60) revealed no neuropathic or cardiac changes on electrocardiogram with daptomycin 6 mg/kg QD for 14 days, 1 patient receiving daptomycin at this dose in another study developed severe acute respiratory syndrome and subsequent acute renal failure possibly related to the study medication.[117] Currently, data using higher doses of daptomycin or the use of daptomycin for longer duration of treatment are limited. As clinical trials continue to gather more information, the safety of such regimens may need to be reassessed.

DRUG INTERACTIONS

Although results from in vitro studies suggest that daptomycin does not inhibit or induce the cytochrome P-450 isozymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4,[24,63] these studies could not determine whether daptomycin may be a substrate for CYP metabolism. The potential for drug interactions between daptomycin and aztreonam, probenecid, warfarin, and simvastatin was investigated in healthy adults.[63] No significant differences were detected in C_{max}, AUC, or total and renal clearance of daptomycin when a single 6-mg/kg dose was administered among 15 healthy adults with a single dose of aztreonam 1000 mg. Similarly, no differences in these parameters were found for daptomycin pharmacokinetics when a single dose of daptomycin 4 mg/kg was administered with probenecid 500 mg QID for 10 doses among 5 healthy adults. The addition of warfarin 25 mg as a single dose on day 5 at steady-state concentrations of daptomycin 6 mg/kg QD (administered for 9 days total) showed no change in pharmacokinetics of daptomycin or warfarin or pharmacodynamic interactions among 16 volunteers.[63]

Coadministration of simvastatin 40 mg/d and daptomycin 4 mg/kg QD for 14 days also did not show any pharmacokinetic differences in plasma trough concentrations of either drug among 20 adults aged >30 years.[63] In this study, CPK concentrations remained within the upper limit of normal (60–400 U/L for males and 40–150 U/L for females) throughout the study. Due to the potential for skeletal muscle toxicity that may result from the pharmacodynamic interaction, the Phase III studies DAP-SST-9801 and DAP-SST-9901 attempted to exclude patients receiving daptomycin and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (ie, statins) simultaneously.[120] However, 34 patients received a statin or fibrate with daptomycin. No significant differences in CPK elevation were seen between patients receiving daptomycin with (2.9% [1/34]) or without (1.0% [5/500]) these antihyperlipidemic agents.[117] Overall, although no dosage adjustment may be suggested, temporary suspension of HMG-CoA reductase inhibitors may be considered during treatment with daptomycin due to concerns regarding myopathy.[24,63]

DOSAGE AND ADMINISTRATION

For the treatment of complicated skin and skin-structure infections, daptomycin should be administered at 4 mg/kg QD in adults.[24] Few data have been collect-

ed to establish the efficacy and safety of higher doses of daptomycin. However, such studies are under way.[120] Based on results of pharmacokinetic studies, no dosage adjustments are recommended for older (aged >75 years) or obese (BMI 25–39 kg/m^2) patients.[24,62,63] Similarly, no dosage adjustment of daptomycin is recommended for the treatment of mild to moderate hepatic impairment. However, the use or pharmacokinetics of daptomycin have not specifically been assessed among patients with severe hepatic impairment (Child-Pugh Class C).[63]

Among the special populations in which pharmacokinetics may be affected by disease state, patients with renal insufficiency may require dosage adjustment of daptomycin. As described in the Pharmacokinetics section, patients with CrCl <30 mL/min or receiving hemodialysis or peritoneal dialysis show 2- to 3-fold greater accumulation of daptomycin (as measured by AUC) than patients with normal renal function.[24,60,62] Reductions in mean clearance rates suggest that the daptomycin dose interval should be extended to daptomycin 4 mg/kg q 48 h for patients with CrCl <30 mL/min, including patients receiving hemodialysis and continuous ambulatory peritoneal dialysis. For patients undergoing dialysis, daptomycin should be administered after the completion of hemodialysis on such therapy days.[24]

Daptomycin is classified as pregnancy category B drug[24]; studies in rats and rabbits at doses up to 75 mg/kg revealed no harm to the fetus. However, no adequate and well-controlled studies have been conducted in pregnant women. Degree of daptomycin excretion in human milk is not known. Thus, daptomycin should be used with caution during pregnancy and lactation.[24] Because all clinical and pharmacokinetic studies to date have been conducted in patients aged ≥18 years, efficacy and safety of daptomycin use in patients aged <18 years have also not been established.[24,120]

Daptomycin is available in single-use vials containing 250 or 500 mg of daptomycin in a sterile, lyophilized, pale yellow to light brown powder. For every 250 mg, daptomycin should be reconstituted in 5 mL of 0.9% sodium chloride for injection. Reconstituted solution should then be diluted in sodium chloride injection and delivered by IV infusion over 30 minutes.[24] Reconstitution and dilution should be conducted using aseptic techniques, as vials do not contain a preservative or bacteriostatic agent. The reconstituted solution is stable for 12 hours at room temperature or 48 hours under refrigeration (2°C–8°C) in the vial. The diluted solution is stable in the infusion bag for the same duration at room temperature or under refrigeration, respectively. However, the total duration of time in the vial and bag should not exceed 12 hours at room temperature or 48 hours under refrigeration.[24] Daptomycin is also compatible in lactated Ringer's solution for injection but not dextrose-containing diluents. Simultaneous administration of other IV medications is not recommended because limited compatibility data have been collected.

PHARMACOECONOMIC CONSIDERATIONS

Daptomycin, linezolid, and quinupristin-dalfopristin were developed to treat resistant gram-positive bacterial infections. Based on the 2004 average wholesale price (in US dollars),[126] the acquisition cost for a 10-day course of daptomycin therapy (4 mg/kg daily [500-mg vials × 10]) is $1681, which is comparable to that of IV linezolid ($1709; 600 mg BID [600-mg vials × 20]) but considerably more expensive than that of vancomycin ($168; 1 g BID [500-mg vials × 40]). In comparison, the cost of treatment with a 10-day course of quinupristin-dalfopristin is $2557 (7.5 mg/kg BID [500-mg vials × 20]). Because of its relatively long half-life (~9 hours), daptomycin is administered QD, which is more convenient for the patient and health care workers.

To date, no pharmacoeconomic analyses of daptomycin have been published. With its high acquisition cost, daptomycin should be reserved for infections due to vancomycin-resistant pathogens or infections caused by gram-positive pathogens that failed to respond to vancomycin therapy.

DISCUSSION

Daptomycin is the first member of a new class of antimicrobial agents known as the cyclic lipopeptides. It causes rapid cell death by disrupting multiple functional aspects of the bacterial plasma membrane, a pharmacologic target that is unique among currently available antimicrobial agents.[27] Because of this unique mechanism of action, cross-resistance with other antibacterial classes is unlikely and has not been reported. The incidence of spontaneous resistance to daptomycin is rare.[93] Of the >1000 subjects who received daptomycin in Phase II/III clinical tri-

als, only 2 confirmed cases of emergence of resistance to daptomycin were reported.[66] In vitro, daptomycin exhibits rapid bactericidal activity against a wide range of clinically important gram-positive pathogens including resistant strains such as ORSA, VISA, VRSA, penicillin-resistant *S pneumoniae*, and VREF.[70–73,75,76] The bactericidal activity of daptomycin appears to be independent of the metabolic status of bacteria (ie, it is active against both dividing and stationary bacteria),[127] making it an attractive choice for the treatment of sequestered high inoculum infections such as endocarditis. Efficacy data from 2 pivotal trials involving a total of 1118 subjects have shown that daptomycin is as efficacious as vancomycin or a semisynthetic penicillin (ie, nafcillin, oxacillin, dicloxacillin, or flucloxacillin) in the treatment of complicated skin and soft tissue infections (daptomycin vs comparator drug: 62.5% vs 60.9% for study DAP-SST-9801 and 80.4% vs 80.5% for study DAP-SST-9901).[120] Clinical trials evaluating the efficacy and tolerability of daptomycin at a dosage of 6 mg/kg QD for staphylococcal bacteremia and endocarditis are ongoing.

Although the incidence of CPK elevations observed in patients treated with daptomycin and comparator drugs was not clinically or statistically different in Phase III clinical trials,[117] daptomycin-induced myopathy has always been a concern. In early clinical trials, 2 of the 5 subjects who received daptomycin at a dosage of 4 mg/kg IV BID developed myopathy after 7 and 11 days, respectively, of dosing. This daptomycin-induced myopathy was mild, nonprogressive, skeletal muscle specific, and readily reversible.[123] In an animal model, Oleson et al[123] reported that daptomycin-related musculoskeletal effects could be minimized with QD administration by allowing for more time between doses for repair of subclinical damages. Whether this daptomycin-induced myopathy in humans could truly be curtailed by QD administration remains unknown. Complicated skin and soft tissue infections are typically treated for 7 to 14 days. Further studies are needed to delineate the long-term AEs on the human musculoskeletal system. It would be prudent to monitor patients for muscle pain or weakness and to obtain CPK levels weekly while undergoing daptomycin therapy. Medications with similar muscle-related AEs, such as HMG-CoA reductase inhibitors, should also be temporarily discontinued if clinically possible.

Daptomycin is highly protein bound (~92%), primarily to albumin.[24] Theoretically, this high degree of protein binding will lead to a low level of free active drug. It has been suggested that clinical failures with daptomycin leading to study suspension in the early 1990s were in part attributable to the high degree of protein binding, although subjects were administered a relatively low dosage of daptomycin (2 mg/kg daily) for the treatment of bacteremia and endocarditis.[46] The clinical relevance of protein binding in daptomycin therapy remains to be elucidated.

Despite these concerns, daptomycin remains a useful addition to the antimicrobial armamentarium. Daptomycin should be reserved for life-threatening situations and/or when multidrug-resistant pathogens are suspected or identified, so that its efficacy for resistant pathogens can be preserved.

CONCLUSIONS

With rapid bactericidal activity, a unique mechanism of action, low incidence of resistance, and a lack of cross-resistance with other antimicrobial agents, daptomycin may be useful in the treatment of not only complicated skin and skin-structure infections but also sequestered high-inoculum infections (eg, endocarditis) due to resistant gram-positive pathogens. However, the use of daptomycin beyond 14 days and at doses >4 mg/kg QD cannot be recommended until clinical efficacy and safety data become available.

REFERENCES

1. Fung HB, Chang JY, Kuczynski S. A practical guide to the treatment of complicated skin and soft tissue infections. *Drugs*. 2003;63:1459–1480.
2. Nichols RL. Optimal treatment of complicated skin and skin structure infections. *J Antimicrob Chemother*. 1999;44(Suppl A):19–23.
3. Reduced susceptibility of *Staphylococcus aureus* to vancomycin–Japan, 1996. *MMWR Morb Mortal Wkly Rep*. 1997;46:624–626.
4. *Staphylococcus aureus* with reduced susceptibility to vancomycin–United States, 1997 [published correction appears in *MMWR Morb Mortal Wkly Rep*. 1997;46:851]. *MMWR Morb Mortal Wkly Rep*. 1997;46:765–766.
5. Update: *Staphylococcus aureus* with reduced susceptibility to vancomycin–United States, 1997 [published

correction appears in *MMWR Morb Mortal Wkly Rep.* 1997;46:851]. *MMWR Morb Mortal Wkly Rep.* 1997;46:813–815.
6. *Staphylococcus aureus* resistant to vancomycin–United States, 2002. *MMWR Morb Mortal Wkly Rep.* 2002;51:565–567.
7. Chang S, Sievert DM, Hageman JC, et al, for the Vancomycin-Resistant *Staphylococcus aureus* Investigative Team. Infection with vancomycin-resistant *Staphylococcus aureus* containing the vanA resistance gene. *N Engl J Med.* 2003;348:1342–1347.
8. Whitener CJ, Park SY, Browne FA, et al. Vancomycin-resistant *Staphylococcus aureus* in the absence of vancomycin exposure. *Clin Infect Dis.* 2004;38:1049–1055.
9. Vancomycin-resistant *Staphylococcus aureus*–Pennsylvania, 2002 [published correction appears in *MMWR Morb Mortal Wkly Rep.* 2002;51:931]. *MMWR Morb Mortal Wkly Rep.* 2002;51:902.
10. Tenover FC, Weigel LM, Appelbaum PC, et al. Vancomycin-resistant *Staphylococcus aureus* isolate from a patient in Pennsylvania. *Antimicrob Agents Chemother.* 2004;48:275–280.
11. Centers for Disease Control and Prevention (CDC). Vancomycin-resistant *Staphylococcus aureus*–New York, 2004. *MMWR Morb Mortal Wkly Rep.* 2004;53:322–323.
12. Das SS, Anderson JR, Macdonald AA, Somerville KW. Endocarditis due to high level gentamicin resistant *Enterococcus faecium*. *J Infect.* 1994;28:185–191.
13. Kauffman CA. Therapeutic and preventative options for the management of vancomycin-resistant enterococcal infections. *J Antimicrob Chemother.* 2003;51 (Suppl 3):iii23–iii30.
14. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990–May 1999, issued June 1999. *Am J Infect Control.* 1999;27:520–532.
15. Gonzales RD, Shreckenberger PC, Graham MB, et al. Infections due to vancomycin-resistant *Enterococcus faecium* resistant to linezolid. *Lancet.* 2001;357:1179.
16. Herrero IA, Issa NC, Patel R. Nosocomial spread of linezolid-resistant, vancomycin resistant *Enterococcus faecium*. *N Engl J Med.* 2002;346:867–869.
17. Auckland C, Teare L, Cooke F, et al. Linezolid-resistant enterococci: Report of the first isolates in the United Kingdom. *J Antimicrob Chemother.* 2002;50:743–746.
18. Tsiodras S, Gold HS, Sakoulas G, et al. Linezolid resistance in a clinical isolate of *Staphylococcus aureus*. *Lancet.* 2001;358:207–208.
19. Schwartz MD, Shive DK, Shaikh ZH. Delayed discovery of linezolid-resistant, vancomycin-resistant *Enterococcus faecium:* Lessons learned. *Clin Infect Dis.* 2004;38:155–156.
20. Rahim S, Pillai SK, Gold HS, et al. Linezolid-resistant, vancomycin-resistant *Enterococcus faecium* infection in patients without prior exposure to linezolid. *Clin Infect Dis.* 2003;36:E146–E148.
21. Jones RN, Della-Latta P, Lee LV, Biedenbach DJ. Linezolid-resistant *Enterococcus faecium* isolated from a patient without prior exposure to an oxazolidinone: Report from the SENTRY Antimicrobial Surveillance Program. *Diagn Microbiol Infect Dis.* 2002;42:137–139.
22. Mutnick AH, Biedenbach DJ, Jones RN. Geographic variations and trends in antimicrobial resistance among *Enterococcus faecalis* and *Enterococcus faecium* in the SENTRY Antimicrobial Surveillance Program (1997–2000). *Diagn Microbiol Infect Dis.* 2003;46:63–68.
23. Center for Drug Evaluation and Research. Application number 21-572. Administrative Document(s). Available at: http://www.fda.gov/cder/foi/nda/2003/21-572_Cubicin_Admindocs_P1.pdf. Accessed October 22, 2004.
24. Cubicin [package insert]. Lexington, Mass: Cubist Pharmaceuticals, Inc.; 2003.
25. Debono M, Abbott BJ, Molloy RM, et al. Enzymatic and chemical modifications of lipopeptide antibiotic A21978C: The synthesis and evaluation of daptomycin (LY146032). *J Antibiot (Tokyo).* 1988;41:1093–1105.
26. Debono M, Barnhart M, Carrell CB, et al. A21978C, a complex of new acidic peptide antibiotics: Isolation, chemistry, and mass spectral structure elucidation. *J Antibiot (Tokyo).* 1987;40:761–777.
27. Silverman JA, Perlmutter NG, Shapiro HM. Correlation of daptomycin bactericidal activity and membrane depolarization in *Staphylococcus aureus*. *Antimicrob Agents Chemother.* 2003;47:2538–2544.
28. Allen NE, Hobbs JN, Alborn WE Jr. Inhibition of peptidoglycan biosynthesis in gram-positive bacteria by LY146032. *Antimicrob Agents Chemother.* 1987;31: 1093–1099.
29. Lakey JH, Lea EJ. The role of acyl chain character and other determinants on the bilayer activity of A21978C an acidic lipopeptide antibiotic. *Biochim Biophys Acta.* 1986;859:219–226.
30. Lakey JH, Maget-Dana R, Ptak M. The lipopeptide antibiotic A21978C has a specific interaction with DMPC only in the presence of calcium ions. *Biochim Biophys Acta.* 1989;985:60–66.

31. Lakey JH, Ptak M. Fluorescence indicates a calcium-dependent interaction between the lipopeptide antibiotic LY146032 and phospholipid membranes. *Biochemistry.* 1988;27:4639–4645.
32. Eliopoulus GM, Willey S, Reiszner E, et al. In vitro and in vivo activity of LY 146032, a new cyclic lipopeptide antibiotic. *Antimicrob Agents Chemother.* 1986;30: 532–535.
33. Jung D, Rozek A, Okon M, Hancock RE. Structural transitions as determinants of the action of the calcium-dependent antibiotic daptomycin. *Chem Biol.* 2004;11: 949–957.
34. Micklefield J. Daptomycin structure and mechanism of action revealed. *Chem Biol.* 2004;11:887–888.
35. Alborn WE Jr, Allen NE, Preston DA. Daptomycin disrupts membrane potential in growing *Staphylococcus aureus. Antimicrob Agents Chemother.* 1991;35:2282–2287.
36. Allen NE, Alborn WE Jr, Hobbs JN Jr. Inhibition of membrane potential-dependent amino acid transport by daptomycin. *Antimicrob Agents Chemother.* 1991;35: 2639–2642.
37. Canepari P, Boaretti M, Lleo MM, Satta G. Lipoteichoic acid as a new target for activity of antibiotics: Mode of action of daptomycin (LY146032). *Antimicrob Agents Chemother.* 1990;34:1220–1226.
38. Boaretti M, Canepari P, Lleo MM, Satta G. The activity of daptomycin on *Enterococcus faecium* protoplasts: Indirect evidence supporting a novel mode of action on lipoteichoic acid synthesis. *J Antimicrob Chemother.* 1993;31:227–235.
39. Boaretti M, Canepari P. Identification of daptomycin-binding proteins in the membrane of *Enterococcus hirae. Antimicrob Agents Chemother.* 1995;39:2068–2072.
40. Canepari P, Boaretti M. Lipoteichoic acid as a target for antimicrobial action. *Microb Drug Resist.* 1996;2:85–89.
41. Laganas V, Alder J, Silverman JA. In vitro bactericidal activities of daptomycin against *Staphylococcus aureus* and *Enterococcus faecalis* are not mediated by inhibition of lipoteichoic acid biosynthesis. *Antimicrob Agents Chemother.* 2003;47:2682–2684.
42. Wale LJ, Shelton AP, Greenwood D. Scanning electron-microscopy of *Staphylococcus aureus* and *Enterococcus faecalis* exposed to daptomycin. *J Med Microbiol.* 1989; 30:45–49.
43. Conrad RS, Howard MJ, Garrison RC, et al. The effects of daptomycin on chemical composition and morphology of *Staphylococcus aureus. Proc Okla Acad Sci.* 1998; 78:15–22.
44. Woodworth JR, Nyhart EH Jr, Brier GL, et al. Single-dose pharmacokinetics and antibacterial activity of daptomycin, a new lipopeptide antibiotic, in healthy volunteers. *Antimicrob Agents Chemother.* 1992;36:318–325.
45. Dvorchik BH, Brazier D, DeBruin MF, Arbeit RD. Daptomycin pharmacokinetics and safety following administration of escalating doses once daily to healthy subjects. *Antimicrob Agents Chemother.* 2003;47:1318–1323.
46. Lee BL, Sachdeva M, Chambers HF. Effect of protein binding of daptomycin on MIC and antibacterial activity. *Antimicrob Agents Chemother.* 1991;35:2505–2508.
47. Louie A, Kaw P, Liu W, et al. Pharmacodynamics of daptomycin in a murine thigh model of *Staphylococcus aureus* infection. *Antimicrob Agents Chemother.* 2001;45: 845–851.
48. Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. *Antimicrob Agents Chemother.* 2004;48:63–68.
49. Caron F, Kitzis MD, Gutmann L, et al. Daptomycin or teicoplanin in combination with gentamicin for treatment of experimental endocarditis due to a highly glycopeptide-resistant isolate of *Enterococcus faecium. Antimicrob Agents Chemother.* 1992;36:2611–2616.
50. Sakoulas G, Eliopoulos GM, Alder J, Eliopoulos CT. Efficacy of daptomycin in experimental endocarditis due to methicillin-resistant *Staphylococcus aureus. Antimicrob Agents Chemother.* 2003;47:1714–1718.
51. Michiels MJ, Bergeron MG. Differential increased survival of staphylococci and limited ultrastructural changes in the core of infected fibrin clots after daptomycin administration. *Antimicrob Agents Chemother.* 1996;40:203–211.
52. Blaser J, Vergeres P, Widmer AF, Zimmerli W. In vivo verification of in vitro model of antibiotic treatment of device-related infection. *Antimicrob Agents Chemother.* 1995;39:1134–1139.
53. Wise R, Gee T, Andrews JM, et al. Pharmacokinetics and inflammatory fluid penetration of intravenous daptomycin in volunteers. *Antimicrob Agents Chemother.* 2002;46:31–33.
54. Vaudaux P, Francois P, Bisognano C, et al. Comparative efficacy of daptomycin and vancomycin in the therapy of experimental foreign body infection due to *Staphylococcus aureus. J Antimicrob Chemother.* 2003;52:89–95.
55. Pryka RD, Novak RM, Wagner DK, Rodvold KA. Clinical pharmacokinetics of daptomycin. *DICP.* 1990; 24:255–256.

56. Woodworth JR, Nybart EH, Wolny JD, et al. Tobramycin and daptomycin disposition when coadministered to healthy volunteers. *J Antimicrob Chemother.* 1994;33:655–659.
57. Rybak MJ, Bailey EM, Lamp KC, Kaatz GW. Pharmacokinetics and bactericidal rates of daptomycin and vancomycin in intravenous drug abusers being treated for gram-positive endocarditis and bacteremia. *Antimicrob Agents Chemother.* 1992;36:1109–1114.
58. Dvorchik B, Arbeit RD, Chung J, et al. Population pharmacokinetics of daptomycin. *Antimicrob Agents Chemother.* 2004;48:2799–2807.
59. Dvorchik B, Sica D, Gehr T. Pharmacokinetics (PK) and safety of single-dose daptomycin in subjects with graded renal insufficiency and end-stage renal disease (ESRD). In: *Abstracts of the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy* [CD-ROM]. San Diego, Calif: American Society for Microbiology; 2002. Abstract A-1387.
60. Sica DA, Gehr T, Dvorchik BH. Pharmacokinetics and safety of single-dose daptomycin in subjects with graded renal insufficiency and end-stage renal disease. In: *Abstracts of the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy* [CD-ROM]. San Diego, Calif: American Society for Microbiology; 2002. Abstract P-2257.
61. Dvorchik B. Moderate liver impairment has no influence on daptomycin pharmacokinetics. *J Clin Pharmacol.* 2004;44:715–722.
62. Dvorchik B, Damphousse D. Single-dose pharmacokinetics of daptomycin in young and geriatric volunteers. *J Clin Pharmacol.* 2004;44:612–620.
63. Center for Drug Evaluation and Research. Approval package for: Application number 21-572. Clinical pharmacology biopharmaceutics review. Available at: http://www.fda.gov/cder/foi/nda/2003/21-572_Cubicin_BioPharmr_P1.pdf. Accessed October 22, 2004.
64. Fuchs PC, Barry AL, Brown SD. Daptomycin susceptibility tests: Interpretive criteria, quality control, and effect of calcium on in vitro tests. *Diagn Microbiol Infect Dis.* 2000;38:51–58.
65. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically.* 6th ed. Wayne, Pa: National Committee for Clinical Laboratory Standards; 2003. Document M7-A6.
66. Center for Drug Evaluation and Research. Approval package for: Application number 21-572. Microbiology review(s). Available at: http://www.fda.gov/cder/foi/nda/2003/21-572_Cubicin_Microbr_P1.pdf. Accessed October 22, 2004.
67. Richter SS, Kealey DE, Murray CT, et al. The in vitro activity of daptomycin against *Staphylococcus aureus* and *Enterococcus* species. *J Antimicrob Chemother.* 2003;52:123–127.
68. Alder J, Li T, Yu D, et al. Analysis of daptomycin efficacy and breakpoint standards in a murine model of *Enterococcus faecalis* and *Enterococcus faecium* renal infection. *Antimicrob Agents Chemother.* 2003;47:3561–3566.
69. Wise R, Andrews JM, Ashby JP. Activity of daptomycin against Gram-positive pathogens: A comparison with other agents and the determination of a tentative breakpoint. *J Antimicrob Chemother.* 2001;48:563–567.
70. Critchley IA, Draghi DC, Sahm DF, et al. Activity of daptomycin against susceptible and multidrug-resistant Gram-positive pathogens collected in the SECURE study (Europe) during 2000–2001. *J Antimicrob Chemother.* 2003;51:639–649.
71. Critchley IA, Blosser-Middleton RS, Jones ME, et al. Baseline study to determine in vitro activities of daptomycin against gram-positive pathogens isolated in the United States in 2000–2001. *Antimicrob Agents Chemother.* 2003;47:1689–1693.
72. Streit JM, Jones RN, Sader HS. Daptomycin activity and spectrum: A worldwide sample of 6737 clinical Gram-positive organisms. *J Antimicrob Chemother.* 2004;53:669–674.
73. Barry AL, Fuchs PC, Brown SD. In vitro activities of daptomycin against 2,789 clinical isolates from 11 North American medical centers. *Antimicrob Agents Chemother.* 2001;45:1919–1922.
74. King A, Phillips I. The in vitro activity of daptomycin against 514 Gram-positive aerobic clinical isolates. *J Antimicrob Chemother.* 2001;48:219–223.
75. Howe RA, Noel AR, Tomaselli S, et al. Killing activity of daptomycin against vancomycin-intermediate *Staphylococcus aureus* (VISA) and hetero-VISA (hVISA). In: *Abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy* [CD-ROM]. Washington, DC: American Society for Microbiology; 2003. Abstract C1-1641.
76. Bozdogan B, Esel D, Whitener C, et al. Antibacterial susceptibility of a vancomycin-resistant *Staphylococcus aureus* strain isolated at the Hershey Medical Center. *J Antimicrob Chemother.* 2003;52:864–868.

77. Klein JD, Ludlam E, Steele-Moore L. In vitro activity of ABT-773, telithromycin and daptomycin against group C and G streptococci. In: *Abstracts of the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy* [CD-ROM]. San Diego, Calif: American Society for Microbiology; 2002. Abstract E-1894.
78. Rybak MJ, Hershberger E, Moldovan T, Grucz RG. In vitro activities of daptomycin, vancomycin, linezolid, and quinupristin-dalfopristin against Staphylococci and Enterococci, including vancomycin-intermediate and -resistant strains. *Antimicrob Agents Chemother.* 2000;44:1062–1066.
79. Cha R, Brown WJ, Rybak MJ. Bactericidal activities of daptomycin, quinupristin-dalfopristin, and linezolid against vancomycin-resistant *Staphylococcus aureus* in an in vitro pharmacodynamic model with simulated endocardial vegetations. *Antimicrob Agents Chemother.* 2003;47:3960–3963.
80. Akins RL, Rybak MJ. Bactericidal activities of two daptomycin regimens against clinical strains of glycopeptide intermediate-resistant *Staphylococcus aureus,* vancomycin-resistant *Enterococcus faecium,* and methicillin-resistant *Staphylococcus aureus* isolates in an in vitro pharmacodynamic model with simulated endocardial vegetations. *Antimicrob Agents Chemother.* 2001;45:454–459.
81. Vance-Bryan K, Larson TA, Rotschafer JC, Toscano JP. Investigation of the early killing of *Staphylococcus aureus* by daptomycin by using an in vitro pharmacodynamic model. *Antimicrob Agents Chemother.* 1992;36: 2334–2337.
82. Silva M, Jacobus NV, Gorbach SL. In vitro activity of LY146032 against gram-positive bacteria. *Diagn Microbiol Infect Dis.* 1988;9:79–85.
83. Bingen E, Doit C, Lambert-Zechovsky N, et al. Bactericidal activity of daptomycin against vancomycin-resistant *Enterococcus faecium* in an in vitro pharmacokinetic model. *Eur J Clin Microbiol Infect Dis.* 1991;10: 1062–1065.
84. Jain R, Schreckenberger PC, Quinn JP, Pendland SL. Bactericidal activity of daptomycin against clinical isolates of linezolid/vancomycin-resistant *Enterococcus faecium.* In: *Abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy* [CD-ROM]. Washington, DC: American Society for Microbiology; 2003. Abstract C1-1643.
85. Pankuch GA, Jacobs MR, Appelbaum PC. Postantibiotic effects of daptomycin against 14 staphylococcal and pneumococcal clinical isolates. *Antimicrob Agents Chemother.* 2003;47:3012–3014.
86. Hanberger H, Nilsson LE, Maller R, Isaksson B. Pharmacodynamics of daptomycin and vancomycin on *Enterococcus faecalis* and *Staphylococcus aureus* demonstrated by studies of initial killing and postantibiotic effect and influence of Ca^{2+} and albumin on these drugs. *Antimicrob Agents Chemother.* 1991;35:1710–1716.
87. Dandekar PK, Tessier PR, Williams P, et al. Pharmacodynamic profile of daptomycin against *Enterococcus* species and methicillin-resistant *Staphylococcus aureus* in a murine thigh infection model. *J Antimicrob Chemother.* 2003;52:405–411.
88. Miniter PM, Patterson TF, Johnson MA, Andriole VT. Activity of LY146032 in vitro and in experimental enterococcal pyelonephritis. *Antimicrob Agents Chemother.* 1987;31:1199–1203.
89. Rand KH, Houck H. Daptomycin synergy with rifampicin and ampicillin against vancomycin-resistant enterococci. *J Antimicrob Chemother.* 2004;53:530–532.
90. Rice LB, Eliopoulos CT, Yao JD, et al. In vivo activity of the combination of daptomycin and fosfomycin compared with daptomycin alone against a strain of *Enterococcus faecalis* with high-level gentamicin resistance in the rat endocarditis model. *Diagn Microbiol Infect Dis.* 1992;15:173–176.
91. Watanakunakorn C. In vitro activity of LY 146032, a novel cyclic lipopeptide, alone and in combination with gentamicin or tobramycin against enterococci. *J Antimicrob Chemother.* 1987;19:445–448.
92. Rand KH, Houck HJ. Synergy of daptomycin with oxacillin and other β-lactams against methicillin-resistant *Staphylococcus aureus. Antimicrob Agents Chemother.* 2004;48:2871–2875.
93. Silverman JA, Oliver N, Andrew T, Li T. Resistance studies with daptomycin. *Antimicrob Agents Chemother.* 2001;45:1799–1802.
94. Snydman DR, McDermott LA, Jacobus NV. Determination of synergistic effects of daptomycin with gentamicin or in vitro effect of beta-lactam antibiotics against *Staphylococcus aureus* and enterococci by FIC index and time-kill kinetics. In: *Abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy* [CD-ROM]. Chicago, Ill: American Society for Microbiology; 2001. Abstract E-533.
95. Kaatz GW, Seo SM. Analysis of the mechanisms of daptomycin resistance in *Staphylococcus aureus.* In:

Abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy [CD-ROM]. Chicago, Ill: American Society for Microbiology; 2001. Abstract C1-1803.

96. Hindes RG, Willey SH, Eliopoulos GM, et al. Treatment of experimental endocarditis caused by a β-lactamase-producing strain of *Enterococcus faecalis* with high-level resistance to gentamicin. *Antimicrob Agents Chemother.* 1989;33:1019–1022.
97. Kaatz GW, Seo SM, Reddy VN, et al. Daptomycin compared with teicoplanin and vancomycin for therapy of experimental *Staphylococcus aureus* endocarditis. *Antimicrob Agents Chemother.* 1990;34:2081–2085.
98. Cantoni L, Glauser MP, Bille J. Comparative efficacy of daptomycin, vancomycin, and cloxacillin for the treatment of *Staphylococcus aureus* endocarditis in rats and role of test conditions in this determination. *Antimicrob Agents Chemother.* 1990;34:2348–2353.
99. Luu QN, Buxton TB, Nelson DR, Rissing JP. Treatment of chronic experimental *Staphylococcus aureus* osteomyelitis with LY146032 and vancomycin. *Eur J Clin Microbiol Infect Dis.* 1989;8: 562–563.
100. Vaudaux P, Schaad H, Francois P, et al. Efficacy of a high-dose regimen of daptomycin compared to oxacillin and vancomycin in the therapy of experimental foreign body infection due to methicillin-susceptible *Staphylococcus aureus.* In: *Abstracts of the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy* [CD-ROM]. San Diego, Calif: American Society for Microbiology; 2002. Abstract 1904.
101. Wood CA, Finkbeiner HC, Kohlhepp SJ, et al. Influence of daptomycin on staphylococcal abscesses and experimental tobramycin nephrotoxicity. *Antimicrob Agents Chemother.* 1989;33:1280–1285.
102. Sapico FL, Ginunas VJ, Canawati HN, Montgomerie JZ. LY146032, alone and in combination with gentamicin, for the treatment of enterococcal pyelonephritis in the rat model. *Antimicrob Agents Chemother.* 1988;32:81–83.
103. Bush LM, Boscia JA, Kaye D. Daptomycin (LY146032) treatment of experimental enterococcal endocarditis. *Antimicrob Agents Chemother.* 1988;32:877–881.
104. Ramos MC, Grayson ML, Eliopoulos GM, Bayer AS. Comparison of daptomycin, vancomycin, and ampicillin-gentamicin for treatment of experimental endocarditis caused by penicillin-resistant enterococci. *Antimicrob Agents Chemother.* 1992;36:1864–1869.
105. Mader JT, Adams K. Comparative evaluation of daptomycin (LY146032) and vancomycin in the treatment of experimental methicillin-resistant *Staphylococcus aureus* osteomyelitis in rabbits. *Antimicrob Agents Chemother.* 1989;33:689–692.
106. Haworth CS, Sobieski MW, Scheld WM, Park TS. *Staphylococcus aureus* ventriculitis treated with single-dose intraventricular vancomycin or daptomycin (LY146032): Bacterial and antibiotic kinetics in hydrocephalic rabbits. *Antimicrob Agents Chemother.* 1990;34:245–251.
107. Kephart PA, Esposito AL. Comparison of the investigational drug, LY146032, with vancomycin in experimental pneumonia due to methicillin-resistant *Staphylococcus aureus. J Antimicrob Chemother.* 1988; 21:33–39.
108. Verghese A, Haire C, Franzus B, Smith K. LY146032 in a hamster model of *Staphylococcus aureus* pneumonia–effect on in vivo clearance and mortality and in vitro opsonophagocytic killing. *Chemotherapy.* 1988;34: 497–503.
109. Dong MY, Chang TW, Gorbach SL. Treatment of *Clostridium difficile* colitis in hamsters with a lipopeptide antibiotic, LY146032. *Antimicrob Agents Chemother.* 1987;31:1135–1136.
110. Li T, Yu D, Mortin LI, et al. Rapid bactericidal action of daptomycin against septicemia induced by gram positive bacteria in mice. In: *Abstracts of the IDSA 40th Annual Meeting* [CD-ROM]. Chicago, Ill: Infectious Diseases Society of America; 2002. Abstract 50.
111. Smith K, Cobbs G, Dill R, et al. Daptomycin versus vancomycin treatment for *Staphylococcus aureus* bacteremia in a murine model. *Chemotherapy.* 1990;36: 428–434.
112. Dougherty SH, Hentges DJ, Casey SW, Thal WR. Impact of LY146032 on *Streptococcus (Enterococcus) faecalis* translocation in mice. *Antimicrob Agents Chemother.* 1988;32:337–340.
113. Beauchamp D, Gourde P, Simard M, Bergeron MG. Subcellular distribution of daptomycin given alone or with tobramycin in renal proximal tubular cells. *Antimicrob Agents Chemother.* 1994;38:189–194.
114. Gurnani K, Khouri H, Couture M, et al. Molecular basis of the inhibition of gentamicin nephrotoxicity by daptomycin; an infrared spectroscopic investigation. *Biochim Biophys Acta.* 1995;1237:86–94.
115. Carrier D, Khalil MB, Kealey A. Modulation of phospholipase A2 activity among aminoglycosides and

daptomycin: A Fourier transform infrared spectroscopy study. *Biochemistry.* 1998:37:7589–7597.
116. Couture M, Simard M, Gourde P, et al. Daptomycin may attenuate experimental tobramycin nephrotoxicity by electrostatic complexation to tobramycin. *Antimicrob Agents Chemother.* 1994;38:742–749.
117. Center for Drug Evaluation and Research. Approval package for: Application number 21-572. Medical Review(s). Available at: http://www.fda.gov/cder/foi/nda/2003/21-572_Cubicin_Medr_P1.pdf. Accessed October 22, 2004.
118. Arbeit RD, Maki D, Tally FP, et al, for the Daptomycin 98-01 and 99-01 Investigators. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. *Clin Infect Dis.* 2004;38:1673–1681.
119. Roditi D, Arbeit RD, the 99-01 Investigators. Clinical significance of dual infection (DI) with *Staphylococcus aureus* (SA) and hemolytic streptococci (hStr) in complicated skin and soft tissue infections (cSSTI): Results from daptomycin (DAP) trial 99-01. In: *Abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy* [CD-ROM]. Chicago, Ill: American Society for Microbiology; 2001. Abstract L-1482.
120. Matthews PA, Debrun ME. Faster resolution of clinical signs (CSx) in complicated skin and soft tissue infection (cSSTI) by daptomycin (DAP) vs standard therapy (STND) in a randomized, blinded, comparative study. In: *Abstracts of the IDSA 39th Annual Meeting* [CD-ROM]. San Francisco, Calif: Infectious Diseases Society of America; 2001. Abstract 112.
121. Snydman DR. Daptomycin. In: *Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy* [CD-ROM]. Toronto, Ont: American Society for Microbiology; 2000. Abstract 1125.
122. Golan Y, Poutsiaka DD, Tozzi S, et al. Daptomycin for line-related *Leuconostoc* bacteraemia. *J Antimicrob Chemother.* 2001;47:364–365.
123. Oleson FB Jr, Berman CL, Kirkpatrick JB, et al. Once-daily dosing in dogs optimizes daptomycin safety. *Antimicrob Agents Chemother.* 2000;44:2948–2953.
124. Knapp AG, Tally FP, Arbeit RD. Skeletal muscle effects in patients receiving once-daily daptomycin (DAP) for complicated skin and skin structure infection (cSSSI). In: *Abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy* [CD-ROM]. Washington, DC: American Society for Microbiology; 2003. Abstract L-736.
125. Kreft B, de Wit C, Krech R, et al. Experimental studies on nephrotoxicity and pharmacokinetics of LY 146032 (daptomycin) in rats. *J Antimicrob Chemother.* 1990;25:635–643.
126. *Drug Topics Red Book.* Montvale, NJ: Thomson Medical Economics; 2004.
127. Hermsen ED, Hovde LB, Hotchkiss JR, Rotschafer JC. Increased killing of staphylococci and streptococci by daptomycin compared with cefazolin and vancomycin in an in vitro peritoneal dialysate model. *Antimicrob Agents Chemother.* 2003;47:3764–3767.

Address correspondence to: Horatio B. Fung, PharmD, BCPS, Critical Care Center, VA Medical Center, 130 West Kingsbridge Road, Bronx, NY 10468. E-mail: horatio.fung@med.va.gov