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Clinical Medicine Reviews in Therapeutics

Pharmacological Agents for the Treatment of Skin and Soft Tissue Infections: What is the Role for Daptomycin?

Theodoros Kelesidis

Department of Medicine, Division of Infectious Diseases, David Geffen School of Medicine, University of California, Los Angeles, CA, USA.

ABSTRACT: Skin and soft tissue infections (SSTIs) have increasing prevalence in clinical practice. The emergence of resistant pathogens and especially methicillin-resistant *Staphylococcus aureus* (MRSA) has led to an increase in the number of hospitalizations due to SSTIs. Daptomycin has been shown to achieve good concentrations in skin and soft tissues and is effective and safe for the treatment of SSTIs. In this review, I summarize the scientific evidence regarding the role of daptomycin in therapy of SSTIs, comparing daptomycin with other antimicrobial agents.

KEYWORDS: daptomycin, skin infections, soft tissue infections, MRSA

CITATION: Kelesidis. Pharmacological Agents for the Treatment of Skin and Soft Tissue Infections: What is the Role for Daptomycin?. *Clinical Medicine Reviews in Therapeutics* 2014:6 7–12 doi: 10.4137/CMRT.S9283.

RECEIVED: December 26, 2013. **RESUBMITTED:** March 2, 2014. **ACCEPTED FOR PUBLICATION:** March 4, 2014.

ACADEMIC EDITOR: Garry Walsh, Editor in Chief

TYPE: Review

FUNDING: Author discloses no funding sources.

COMPETING INTERESTS: Author discloses no potential conflicts of interest.

CORRESPONDENCE: tkelesidis@mednet.ucla.edu

Introduction

Skin and soft tissue infections (SSTIs) have increasing prevalence and are among the most common infections in clinical practice. The emergence of resistant isolates, especially methicillin-resistant *Staphylococcus aureus* (MRSA), has led to an increase in the number of hospitalizations due to SSTIs. SSTIs caused by multidrug-resistant isolates are difficult to treat, and often require patient hospitalization and use of intravenous antibiotics.[1–3] SSTIs are associated with increased patient age and relevant comorbidities, obesity, diabetes, prior surgery, and decreased mobilization,[4,5] are also associated with prolonged hospitalization of patients, indirectly affecting morbidity and mortality.[6] Such infections tend to relapse and may cause many complications.[7,8] The type and extent of the SSTI represent other important predictors for the outcome of these infections, which can be classified according to the severity of systemic and local signs and symptoms of infection[9] or can be defined as complicated (cSSTIs) or noncomplicated based on the need for surgical intervention, the extent of the disease, and the presence of systemic manifestations.[9] Thus, SSTIs that require surgical intervention, deeper SSTIs, major abscesses, and acute and chronic wound infections (including diabetic foot infections) are all considered cSSTIs.[9,10] Although these terms have previously been used in practice guidelines,[11] the term acute bacterial skin and skin structure infections (ABSSSI), previously referred to as uncomplicated and complicated skin and skin structure infections has increasingly been used.[12] Herein, the term cSSTI will be used according to published practice guidelines.[11] Various antibiotics that are commonly used against SSTIs, especially cSSTIs and those caused by MRSA, have high treatment success rates.[9,10] According to practice guidelines, vancomycin, linezolid, or daptomycin should be used for treatment of cSSTIs (A-I recommendation).[11] However, the prevalence of antibiotic-resistant Gram-positive bacteria such as vancomycin-resistant enterococci (VRE) and MRSA continues to increase.[13] Many institutions across the developed countries may have increased (>50%) rates of MRSA.[14] Despite the development of new antimicrobial agents, treatment of antibiotic-resistant Gram-positive bacteria remains a challenge.[13,15] Although vancomycin continues to be the mainstay for treatment of MRSA, increased failures have been described.[16,17] One of the available alternatives to vancomycin therapy that has demonstrated in vitro and in vivo activity against MRSA and VRE is daptomycin.[18] Daptomycin,

a fermentation product of *Streptomyces roseosporus*, is a first-in-class acidic lipopeptide antibiotic that possesses potent in vitro bactericidal activity against multidrug-resistant Gram-positive bacteria, including resistant strains such as MRSA, glycopeptide-intermediate *S. aureus* (GISA), vancomycin-resistant *S. aureus* (VRSA), penicillin-resistant streptococci, and VRE.[18–20,21] Initiation of clinical trials in 1999[22] led to the approval of daptomycin by the US Food and Drug Administration (FDA) in 2003 at single daily doses of 4 mg/kg for the treatment of cSSSIs caused by susceptible strains.[23] In 2006, it was approved in the United States for the treatment of *S. aureus* bacteremia, including right-sided infective endocarditis, at a dosage of 6 mg/kg given once daily.[22] Unfortunately, clinical failures and resistant strains have been reported with daptomycin.[24–26] Daptomycin has good concentrations in skin and soft tissues and may have a major role for treatment of SSTIs.[27,28] In this manuscript, I review the available scientific evidence regarding the role of daptomycin in treatment of SSTIs.

Mechanism of Action and Pharmacokinetic Profile

Daptomycin is bactericidal and effective against most Gram-positive pathogens, including those with multidrug resistance.[22,23] The mechanism of action of daptomycin is different from other antibiotics.[15] Daptomycin binds to bacterial membranes in a calcium-dependent manner, leading to cellular leakage and death and causes channel formation within the cell wall, enabling the efflux of potassium with rapid depolarization of the membrane potential,[15] which leads to inhibition of protein, DNA, and RNA synthesis, causing bacterial cell death.[23] Daptomycin exhibits concentration-dependent activity rather than time-dependent activity (time the drug concentration exceeds the Minimal Inhibitory Concentration (MIC)).[29] Thus, the area under the concentration–time curve from 0 to 24 hours (AUC_{0-24}) and the peak concentration (C_{max}) are the parameters that best correlate with the efficacy of daptomycin.[29] Pharmacodynamic animal model data indicated that a once-daily regimen should be as effective as a fractionated regimen with the same total daily dose.[30] Following intravenous administration, daptomycin exhibits generally linear pharmacokinetics at doses of 4–12 mg/kg every 24 hours (q24h).[23] As the drug is 90–93% reversibly bound to human plasma proteins, the concentration of free drug achieved in tissues and the MIC breakpoints for Gram-positive bacteria should be taken into consideration since there is increased risk of development of resistance at doses at which the minimum concentration (C_{min}) is at or below the breakpoint.[31] The concentration-dependent activity of daptomycin, its linear pharmacokinetics and favorable safety profile have favored the use of high doses of daptomycin to increase efficacy.[29,31]

Clinical Studies Regarding Efficacy of Daptomycin for Treatment of cSSTI

Overall efficacy of daptomycin for treatment of cSSTI compared to vancomycin and β-lactams. Daptomycin is known to be effective for the treatment of cSSTI. A meta-analysis based on randomized controlled trials (RCTs) has determined the comparative efficacy of daptomycin for the treatment of cSSTI.[32] This meta-analysis included a total of 688 patients in the daptomycin group and 869 in the β-lactam/vancomycin group, who received at least one dose of the studied regimens. Only four studies were identified that met the inclusion criteria. Although daptomycin was associated with more rapid clinical cure, overall success was similar for daptomycin compared with vancomycin or β-lactams for the treatment of cSSTI in the clinically evaluable patients [(84.8%) vs 86.2%; OR 0.89; 95% CI 0.63–1.25 in three RCTs), or intention-to-treat (ITT) populations [73.6 vs 85.5%; OR 0.98; 95% CI 0.77–1.26).[33–35] Clinical success was similar in patients who were treated with daptomycin versus vancomycin.[33,34,36] There was no significant difference in clinical success rates when the study with uncomplicated infections was excluded[33–35] or when all four studies were analyzed, including the nonrandomized study.[33,34,36]

Efficacy of daptomycin for treatment of MRSA cSSTI. Guidelines suggest that because of the high prevalence of community-associated MRSA strains, patients who present with serious SSI infections that are possibly caused by staphylococci, should be assumed to have MRSA until proven otherwise. Daptomycin, linezolid, and vancomycin are agents with potent anti-MRSA activity that should be reserved for patients who have severe infections or those who have not responded to initial antimicrobial therapy[11] and should also be the drug of choice for surgical infections in hospitals with high MRSA prevalence. Guidelines also suggest that daptomycin may be used for treatment of MRSA diabetic foot infections.[37] Daptomycin exhibits concentration-dependent activity. Currently, the daptomycin dosage is 4 mg/kg/day for treatment of cSSTI, however higher doses (>6 mg/kg/day) have been used as a possible alternative.[38] In vitro data suggest that higher doses of daptomycin may suppress the emergence of daptomycin resistance and demonstrate rapid bactericidal activity.[38] Clinical trials and retrospective case studies have documented the safety and tolerability of high-dose daptomycin, even when administered for a prolonged duration.[38] In a RCT study of high-dose short duration (10 mg/kg every 24 hours for four days) daptomycin vs. standard of care therapy with vancomycin or semisynthetic penicillin for the treatment of patients with cSSTI caused by Gram-positive bacteria, daptomycin did not demonstrate superior efficacy to other treatments.[34] Data from RCTs comparing high dose (>6 mg/kg) versus standard dose (4 mg/kg) of daptomycin for treatment of SSTI are lacking but retrospective case control studies with limitations have shown possible increased efficacy with high-dose daptomycin compared with standard-dose daptomycin.[39] cSSTIs were the second most common infection type in patients treated with daptomycin doses ≥8 mg/kg analyzed in a retrospective registry (the Cubicin Outcomes Registry and Experience database).[14] From the EU-CORE

analysis of high-dose daptomycin, 52 patients (19%) had SSTIs and clinical success was achieved in 85% of patients.[31] Further RCTs are needed to evaluate the efficacy of high-dose daptomycin in treatment of SSTIs.

Regarding comparative efficacy of daptomycin in patients with MRSA infections, no concrete conclusions can be drawn from the reviewed studies.[32] There were considerable differences between RCT in the proportion of patients who were infected with MRSA. Two RCT studies comparing daptomycin with vancomycin for treatment of cSSTI evaluated microbiologic and clinical success in the subgroup with MRSA infections but there were no significant differences between the comparison groups.[33,34] In addition, clinical success was considerably lower in MRSA-infected patients than in the rest of the patients with SSTIs, in both treatment arms.[33,34] Overall, daptomycin was not superior over other regimens in this group of patients.

Effect of daptomycin on duration of therapy in SSTI. The time needed for an antimicrobial to treat SSTIs plays a major role in decreasing the length of hospitalization for patients.[40] Studies have suggested that with the use of daptomycin, fewer patients would need to receive prolonged intravenous therapy and could be discharged earlier with earlier switch to oral antibiotics compared to other intravenous regimens.[33,36] A nonrandomized study failed to answer whether daptomycin can be used to decrease duration of therapy in cSSTIs because of its study design in which the patients in the control group had MRSA SSTIs, which are known to increase the duration of therapy.[41] On the other hand, the results of another study high MRSA prevalence indicate that four days of intravenous therapy with high-dose daptomycin are equivalent to eight days of intravenous therapy with vancomycin with a no statistically significant trend toward better results with eight-day regimens.[34] In a RCT with uncomplicated SSTIs patients, the use of daptomycin had no significant benefit regarding duration of therapy.[35] In another study, significantly fewer patients needed prolonged (>1 week) therapy in the daptomycin versus the comparator arm.[33] In a nonrandomized study, hospital length of stay of patients in the daptomycin group was shorter compared to the control group.[36] In a retrospective study among patients with a successful outcome, the duration of treatment with daptomycin was not significantly different for MRSA and MSSA patient.[42] Overall, there is limited evidence to suggest that daptomycin may reduce the duration of intravenous treatment in cSSTIs[32] and further prospective studies are needed to define the optimal dosage and duration of therapy with daptomycin in cSSTIs.

Safety of daptomycin. In a recent meta-analysis, various adverse events possibly or probably related to daptomycin treatment were reported in the analyzed studies.[32] The number of patients who had daptomycin-related side events ranged from 0–42% but there was variability in the definitions of adverse events between studies.[34,36] Nausea, vomiting, dizziness, muscle toxicity, and rash were the most common adverse events but there were no statistically significant differences in the incidence of adverse effects between different treatment groups.[33–36] Regarding all-cause mortality, in one study, eight patients in each treatment group died,[33] whereas in the other RCT studies, no deaths occurred.[33–36] Thus, no differences in toxicity between different treatments for cSSTI have been reported. Daptomycin seems to have similar safety profile compared to vancomycin and β-lactam antibiotics with regard to major toxicity events.[32] Of note, the higher incidence of reported toxicity that was observed in the daptomycin group compared to the control group in one study may be associated with the use of a higher daptomycin dose in this small study.[34] However, since such toxicity is rare, a larger population of patients would be needed to accurately detect differences in toxicities between the antimicrobials. Although daptomycin has the potential for significant muscle toxicity, based on the relative lack of severe nephrotoxicity, this drug can be considered as an alternative to other antimicrobials such as vancomycin and semisynthetic penicillins. Although clinical trial data of daptomycin doses >6 mg/kg are limited, clinical experience reported to date and evidence from case reports, retrospective studies, case series, phase-1 clinical trials, and randomized controlled clinical trials suggest that daptomycin is effective and well tolerated at higher doses.[31]

Muscle toxicity. In the initial phase-1 trials, daptomycin was well tolerated in healthy volunteers at up to 6 mg/kg IV in two divided doses per day.[43] However, when a higher dosage 8 mg/kg per day in two divided doses was used for safety testing in a phase-1study, two of five volunteers developed increases in creatine phosphokinase (CPK) levels.[44] Two different phase-1 trials involving healthy volunteers demonstrated that once-daily administration of daptomycin at doses of 8–12 mg/kg caused no symptoms of adverse effects involving the musculoskeletal system or elevations in CPK level in any study participant after 14 days of treatment,[19,45] demonstrating that the once-daily regimen minimized the potential for daptomycin-associated adverse effects involving the musculoskeletal system. In phase-3 trials involving cSSSI, CPK level elevations occurred in 2.8% of patients in the daptomycin-treated group, compared with 1.8% in the controls[22] and the proportion of patients with adverse effects involving the musculoskeletal system and connective tissue was actually higher in the comparator group (36.2%) than in the daptomycin group (29.2%).[22] Based on these studies, daptomycin dosages of 4 mg/kg per day are indicated as safe and effective for treatment of cSSSI.[22] However, the probability of creatinine phosphokinase elevation and musculoskeletal adverse events are related with higher daptomycin C_{min} concentrations[46] and patients needs to be monitored closely for muscle toxicity if higher doses of daptomycin are used.

Daptomycin-induced acute eosinophilic pneumonia (AEP). Of greater concern were the reports of daptomycin-induced AEP in 2010[47,48] following the review of 42 cases (7 likely and 36 possible) from FDA.[49] Based on the FDA's

Adverse Event Reporting System database, the incidence of daptomycin-induced AEP is small and approximately 0.43 per 10,000 patients treated. The syndrome is characterized by the presence of new lung infiltrates and hypoxia and eosinophilia in bronchoalveolar samples.[47,48] Peripheral eosinophilia and rash may be absent. The role of steroids is unclear but daptomycin should be withheld in patients developing new infiltrates while pending further investigations.

Daptomycin Resistance

Following approval, clinical failures and the emergence of resistant strains have been reported.[50] However, daptomycin has a low frequency of development of resistance in vitro, and more than 99% of *S. aureus* isolates were susceptible in large surveillance studies.[51,52] Daptomycin resistance is often associated with reduced susceptibility to vancomycin, especially in patients with prior vancomycin use.[53] Clinical data from the retrospective daptomycin registry, Cubicin Outcomes Registry and Experience suggest that patients failing vancomycin were more likely to fail daptomycin salvage therapy compared with patients switched for other reasons.[54] However, no instances of development of resistance were reported in two RCTs regarding the use of daptomycin for treatment of cSSTI, although there were a large number of isolates with increase in the MIC of daptomycin after therapy.[33,34] Ongoing surveillance is needed to accurately estimate this risk.

In an attempt to prevent resistance selection, higher doses of daptomycin have been suggested and studied. Better therapeutic outcomes were achieved with higher doses of daptomycin (8 mg/kg) compared with lower doses (4–6 mg/kg).[39] However, the probability of an adverse event increases with higher doses and patients should thus be monitored closely if higher doses of daptomycin are used for treatment of cSSTI.

The Role of Daptomycin in Treatment of STTIs in the Outpatient Practice

Outpatient parenteral antibiotic therapy (OPAT) for SSTIs is cost-effective since hospitalization may be either avoided or reduced.[55,56] Once-daily administration, activity against MRSA, and proven clinical efficacy in cSSTIs and its safety profile make daptomycin ideal for outpatient administration.[57] In addition, bolus IV administration has comparable pharmacokinetics and safety profile to a 30 minute infusion, which may further enhance the utility of daptomycin in the outpatient setting.[58,59] Use of daptomycin, at least in part, in the outpatient setting for cSSTIs has been associated with excellent clinical success and early discharge was associated with hospital-charge savings.[59–61] In a retrospective analysis of clinical and cost outcomes associated with MRSA, cSSI treated with daptomycin, vancomycin, or linezolid, the length of hospitalization was slightly shorter in the daptomycin group.[62] Thus, although data from randomized controlled clinical trials comparing outpatient use of daptomycin to oral linezolid are lacking, daptomycin has a major role in the treatment of STTIs in the outpatient practice.[57]

Limitations of Studies that have Assessed the Efficacy of Daptomycin for Treatment of cSSTI

There are several limitations regarding the studies that have compared daptomycin with other antimicrobials for treatment of cSSTI such as limited number of studies, suboptimal (eg, nonrandomized) study design in many of them.[36] In some studies, the patient population had only mild infections[35] whereas there are variations in the definitions of clinical success between different studies.

These studies did not have similar definitions of outcomes and the duration of therapy was often different. However since most patients with SSTIs are cured by the use of other antimicrobial regimens, a large number of patients will be needed to prove statistically that daptomycin is superior to other antimicrobials, if there is a small additional benefit by the use of daptomycin. In addition, more studies are needed in patients with SSTIs with lower success rates such as those caused by MRSA.[33,63,64]

Conclusion

In conclusion, recent data suggest that daptomycin is an effective antimicrobial agent for the treatment of SSTIs. Daptomycin was equally safe regarding major adverse events compared to vancomycin and semisynthetic penicillins. The current literature on a high-dose daptomycin treatment strategy suggests improved in vitro efficacy safety and tolerability, even when given for extended durations. However, evidence from randomized, prospective clinical trials in large populations in support of improved in vivo efficacy of daptomycin compared to other antimicrobials such as vancomycin or linezolid is still lacking. Once-daily dosing allows ease of use in both hospital and outpatient settings, is cost-effective, and may facilitate early discharge or avoided admission in some patient groups with SSTIs.[57] Further research is needed to identify the optimal dose of daptomycin and duration of therapy for cSSTIs and randomized controlled clinical trials comparing daptomycin to other antimicrobials such as oral linezolid are needed to further define the role of daptomycin in the treatment of STTIs in the outpatient practice.

Author Contributions

Conceived the concept: TK. Analyzed the data: TK. Wrote the first draft of the manuscript: TK. Made critical revisions: TK. The author reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the author has provided signed confirmation of compliance with ethical and legal obligations including but not limited to compliance with

ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the author was invited to submit this paper.

REFERENCE

1. Rajendran PM, Young D, Maurer T, et al. Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community-acquired methicillin-resistant *Staphylococcus aureus* infection. *Antimicrob Agents Chemother*. 2007;51(11):4044–8.
2. Ruhe JJ, Smith N, Bradsher RW, Menon A. Community-onset methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections: impact of antimicrobial therapy on outcome. *Clin Infect Dis*. 2007;44(6):777–84.
3. King MD, Humphrey BJ, Wang YF, et al. Emergence of community-acquired methicillin-resistant *Staphylococcus aureus* USA 300 clone as the predominant cause of skin and soft-tissue infections. *Ann Intern Med*. 2006;144(5):309–17.
4. Hersh AL, Chambers HF, Maselli JH, Gonzales R. National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. *Arch Intern Med*. 2008;168(14):1585–91.
5. Johnson JK, Khoie T, Shurland S, et al. Skin and soft tissue infections caused by methicillin-resistant *Staphylococcus aureus* USA300 clone. *Emerg Infect Dis*. 2007;13(8):1195–200.
6. Conly JM, Stiver HG, Weiss KA, et al. A retrospective analysis of practice patterns in the treatment of methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections at three Canadian tertiary care centres. *Can J Infect Dis*. 2003;14(6):315–21.
7. Chou YY, Lin TY, Lin JC, et al. Vancomycin-resistant enterococcal bacteremia: comparison of clinical features and outcome between *Enterococcus faecium* and *Enterococcus faecalis*. *J Microbiol Immunol Infect*. 2008;41(2):124–9.
8. Szumowski JD, Cohen DE, Kanaya F, Mayer KH. Treatment and outcomes of infections by methicillin-resistant *Staphylococcus aureus* at an ambulatory clinic. *Antimicrob Agents Chemother*. 2007;51(2):423–8.
9. Eron LJ, Lipsky BA, Low DE, et al. Managing skin and soft tissue infections: expert panel recommendations on key decision points. *J Antimicrob Chemother*. 2003;52(suppl 1):i3–17.
10. Eisenstein BI. Treatment challenges in the management of complicated skin and soft-tissue infections. *Clin Microbiol Infect*. 2008;14(suppl 2):17–25.
11. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis*. 2005;41(10):1373–406.
12. Moran GJ, Abrahamian FM, Lovecchio F, Talan DA. Acute bacterial skin infections: developments since the 2005 Infectious Diseases Society of America (IDSA) guidelines. *J Emerg Med*. 2013;44(6):e397–412.
13. Farrell DJ, Mendes RE, Ross JE, Jones RN. Linezolid surveillance program results for 2008 (LEADER Program for 2008). *Diagn Microbiol Infect Dis*. 2009;65(4):392–403.
14. Moise PA, Hershberger E, Amodio-Groton MI, Lamp KC. Safety and clinical outcomes when utilizing high-dose (> or = 8 mg/kg) daptomycin therapy. *Ann Pharmacother*. 2009;43(7):1211–9.
15. Akins RL, Haase KK. Gram-positive resistance: pathogens, implications, and treatment options: insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2005;25(7):1001–10.
16. Soriano A, Marco F, Martínez JA, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2008;46(2):193–200.
17. Sakoulas G, Moise-Broder PA, Schentag J, et al. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol*. 2004;42(6):2398–402.
18. Tedesco KL, Rybak MJ. Daptomycin. *Pharmacotherapy*. 2004;24(1):41–57.
19. 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(4):1318–23.
20. Tally FP, DeBruin MF. Development of daptomycin for Gram-positive infections. *J Antimicrob Chemother*. 2000;46(4):523–6.
21. Cha R, Grucz RG Jr, Rybak MJ. Daptomycin dose-effect relationship against resistant Gram-positive organisms. *Antimicrob Agents Chemother*. 2003;47(5):1598–603.
22. Carpenter CF, Chambers HF. Daptomycin: another novel agent for treating infections due to drug-resistant Gram-positive pathogens. *Clin Infect Dis*. 2004;38(7):994–1000.
23. Eisenstein BI, Oleson FB Jr, Baltz RH. Daptomycin: from the mountain to the clinic, with essential help from Francis Tally, MD. *Clin Infect Dis*. 2010;50(suppl 1):S10–5.
24. Julian K, Kosowska-Shick K, Whitener C, et al. Characterization of a daptomycin-nonsusceptible vancomycin-intermediate *Staphylococcus aureus* strain in a patient with endocarditis. *Antimicrob Agents Chemother*. 2007;51(9):3445–8.
25. Hidron AI, Schuetz AN, Nolte FS, Gould CV, Osborn MK. Daptomycin resistance in *Enterococcus faecalis* prosthetic valve endocarditis. *J Antimicrob Chemother*. 2008;61(6):1394–6.
26. Lewis JS, Owens A, Cadena J, et al. Emergence of daptomycin resistance in *Enterococcus faecium* during daptomycin therapy. *Antimicrob Agents Chemother*. 2005;49(4):1664–5.
27. Jeu L, Fung HB. Daptomycin: a cyclic lipopeptide antimicrobial agent. *Clin Ther*. 2004;26(11):1728–57.
28. Kim A, Suecof LA, Sutherland CA, et al. In vivo microdialysis study of the penetration of daptomycin into soft tissues in diabetic versus healthy volunteers. *Antimicrob Agents Chemother*. 2008;52(11):3941–6.
29. Sauermann R, Rothenburger M, Graninger W, Joukhadar C. Daptomycin: a review 4 years after first approval. *Pharmacology*. 2008;81(2):79–91.
30. Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. *Antimicrob Agents Chemother*. 2004;48(1):63–8.
31. Gould IM, Miro JM, Rybak MJ. Daptomycin: the role of high-dose and combination therapy for Gram-positive infections. *Int J Antimicrob Agents*. 2013;42(3):202–10.
32. Bliziotis IA, Plessa E, Peppas G, Falagas ME. Daptomycin versus other antimicrobial agents for the treatment of skin and soft tissue infections: a meta-analysis. *Ann Pharmacother*. 2010;44(1):97–106.
33. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. *Clin Infect Dis*. 2004;38(12):1673–81.
34. Katz DE, Lindfield KC, Steenbergen JN, et al. A pilot study of high-dose short duration daptomycin for the treatment of patients with complicated skin and skin structure infections caused by Gram-positive bacteria. *Int J Clin Pract*. 2008;62(9):1455–64.
35. Pertel PE, Eisenstein BI, Link AS, et al. The efficacy and safety of daptomycin vs. vancomycin for the treatment of cellulitis and erysipelas. *Int J Clin Pract*. 2009;63(3):368–75.
36. Davis SL, McKinnon PS, Hall LM, et al. Daptomycin versus vancomycin for complicated skin and skin structure infections: clinical and economic outcomes. *Pharmacotherapy*. 2007;27(12):1611–8.
37. Lipsky BA, Berendt AR, Embil J, de LF. Diagnosing and treating diabetic foot infections. *Diabetes Metab Res Rev*. 2004;20(suppl 1):S56–64.
38. Abraham G, Finkelberg D, Spooner LM. Daptomycin-induced acute renal and hepatic toxicity without rhabdomyolysis. *Ann Pharmacother*. 2008;42(5):719–21.
39. Bassetti M, Nicco E, Ginocchio F, et al. High-dose daptomycin in documented *Staphylococcus aureus* infections. *Int J Antimicrob Agents*. 2010;36(5):459–61.
40. Cosgrove SE, Qi Y, Kaye KS, et al. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. *Infect Control Hosp Epidemiol*. 2005;26(2):166–74.
41. Silverman JA, Oliver N, Andrew T, Li T. Resistance studies with daptomycin. *Antimicrob Agents Chemother*. 2001;45(6):1799–802.
42. Martone WJ, Lamp KC. Efficacy of daptomycin in complicated skin and skin-structure infections due to methicillin-sensitive and -resistant *Staphylococcus aureus*: results from the CORE Registry. *Curr Med Res Opin*. 2006;22(12):2337–43.
43. Woodworth JR, Nyhart EH Jr, Brier GL, Wolny JD, Black HR. Single-dose pharmacokinetics and antibacterial activity of daptomycin, a new lipopeptide antibiotic, in healthy volunteers. *Antimicrob Agents Chemother*. 1992;36(2):318–25.
44. Tally FP, Zeckel M, Wasilewski MM, et al. Daptomycin: a novel agent for Gram-positive infections. *Expert Opin Investig Drugs*. 1999;8(8):1223–38.
45. Benvenuto M, Benziger DP, Yankelev S, Vigliani G. Pharmacokinetics and tolerability of daptomycin at doses up to 12 milligrams per kilogram of body weight once daily in healthy volunteers. *Antimicrob Agents Chemother*. 2006;50(10):3245–9.
46. Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. *Clin Infect Dis*. 2010;50(12):1568–74.
47. Miller BA, Gray A, Leblanc TW, et al. Acute eosinophilic pneumonia secondary to daptomycin: a report of three cases. *Clin Infect Dis*. 2010;50(11):e63–8.
48. Lal Y, Assimacopoulos AP. Two cases of daptomycin-induced eosinophilic pneumonia and chronic pneumonitis. *Clin Infect Dis*. 2010;50(5):737–40.
49. van Hal SJ, Paterson DL. New Gram-positive antibiotics: better than vancomycin? *Curr Opin Infect Dis*. 2011;24(6):515–20.
50. van Hal SJ, Paterson DL, Gosbell IB. Emergence of daptomycin resistance following vancomycin-unresponsive *Staphylococcus aureus* bacteraemia in a daptomycin-naive patient—a review of the literature. *Eur J Clin Microbiol Infect Dis*. 2011;30(5):603–10.
51. Pfaller MA, Sader HS, Jones RN. Evaluation of the in vitro activity of daptomycin against 19615 clinical isolates of Gram-positive cocci collected in North American hospitals (2002–2005). *Diagn Microbiol Infect Dis*. 2007;57(4):459–65.

52. Sader HS, Streit JM, Fritsche TR, Jones RN. Antimicrobial susceptibility of Gram-positive bacteria isolated from European medical centres: results of the Daptomycin Surveillance Programme (2002–2004). *Clin Microbiol Infect*. 2006;12(9):844–52.
53. Cui L, Isii T, Fukuda M, et al. An RpoB mutation confers dual heteroresistance to daptomycin and vancomycin in *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2010;54(12):5222–33.
54. Crompton JA, North DS, Yoon M, et al. Outcomes with daptomycin in the treatment of *Staphylococcus aureus* infections with a range of vancomycin MICs. *J Antimicrob Chemother*. 2010;65(8):1784–91.
55. Seaton RA, Bell E, Gourlay Y, Semple L. Nurse-led management of uncomplicated cellulitis in the community: evaluation of a protocol incorporating intravenous ceftriaxone. *J Antimicrob Chemother*. 2005;55(5):764–7.
56. Tice AD, Rehm SJ, Dalovisio JR, et al. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines. *Clin Infect Dis*. 2004;38(12):1651–72.
57. Seaton RA. Daptomycin: rationale and role in the management of skin and soft tissue infections. *J Antimicrob Chemother*. 2008;62(suppl 3):iii15–23.
58. Chakraborty A, Roy S, Loeffler J, Chaves RL. Comparison of the pharmacokinetics, safety and tolerability of daptomycin in healthy adult volunteers following intravenous administration by 30 min infusion or 2 min injection. *J Antimicrob Chemother*. 2009;64(1):151–8.
59. Fossaceca C. Outcomes analysis of daptomycin use in a community hospital. *Adv Ther*. 2007;24(3):517–28.
60. Seaton RA, Macconnachie AA. Experience with daptomycin in an infectious diseases service over 1 year: utility in an outpatient parenteral antibiotic programme. *Int J Antimicrob Agents*. 2008;31(5):492–7.
61. Martone WJ, Lindfield KC, Katz DE. Outpatient parenteral antibiotic therapy with daptomycin: insights from a patient registry. *Int J Clin Pract*. 2008;62(8):1183–7.
62. Wright BM, Eiland EH III. Retrospective analysis of clinical and cost outcomes associated with methicillin-resistant *Staphylococcus aureus* complicated skin and skin structure infections treated with daptomycin, vancomycin, or linezolid. *J Pathog*. 2011;2011:347969.
63. Chirurgi VA, Edelstein H, Oster SE, et al. Randomized comparison trial of teicoplanin i.v., teicoplanin i.m., and cefazolin therapy for skin and soft tissue infections caused by Gram-positive bacteria. *South Med J*. 1994;87(9):875–80.
64. Weigelt J, Itani K, Stevens D, et al. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. *Antimicrob Agents Chemother*. 2005;49(6):2260–6.