Daptomycin for Methicillin-Resistant *Staphylococcus aureus* Diabetic Foot Infections

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**Background:** Diabetic foot infection (DFI) is a serious, difficult-to-treat infection, especially when caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin has been the standard treatment for MRSA infection, but lower response rates in MRSA skin infections have been reported. This analysis assessed the outcome and safety of daptomycin therapy in patients with a DFI caused by MRSA.

**Methods:** Using the Cubicin Outcomes Registry and Experience and the European Cubicin Outcomes Registry and Experience (2006–2009), 79 patients with MRSA DFI were identified and included in this analysis.

**Results:** In the 74 evaluable patients, daptomycin was administered at a median dose of 4.8 mg/kg primarily every 24 hours (85.1%) and for a median of 15.0 days. Overall, 77.0% of the patients (57 of 74) received initial therapy with activity against MRSA; however, of patients receiving daptomycin as second-line therapy (n = 31), only 45.2% were treated with an antibiotic agent active against MRSA. The overall clinical success and treatment failure rates were 89.2% and 10.8%, respectively. Success with daptomycin therapy was higher in patients who had surgery and in those whose initial therapy was daptomycin. Eleven patients had 14 adverse events, two of which were possibly related to daptomycin use and led to discontinuation.

**Conclusions:** In a large real-world cohort of patients with MRSA DFI, daptomycin therapy was shown to be generally well tolerated and effective. The use of an anti-MRSA antibiotic agent should be considered when implementing first-line antibiotic drug therapy for DFI in countries where MRSA is common to avoid inappropriate empirical treatment and potential negative effects on outcomes. (J Am Podiatr Med Assoc 104(2): 159-168, 2014)

Foot infections in people with diabetes are common, resulting in an age-adjusted hospital discharge rate of 5.7 per 1,000 diabetic patients for ulcers in 2007 in the United States. In the United Kingdom, the annual incidence of diabetic foot infections (DFIs) varies from 1.0% to 3.6%, with a prevalence of 5%. Results from the Eurodiale Study, a pan-European collaborative network of 14 European diabetic foot centers, estimated an average of 2.30 weeks per hospitalization-person (N = 1,088). In addition, the total direct and indirect cost associated with DFIs was €10,091 (2005) per person (N = 821). Also, DFIs are among the most difficult complicated skin and skin structure infections (cSSSIs) to treat. The difficulty in managing DFIs is suggested by the 2010 guidance by the US Food and Drug Administration regarding the clinical
development of drugs for the treatment of acute bacterial SSSIs (ABSSSIs). Diabetic foot infections are specifically excluded from this guidance because this infection type requires “more complex treatment regimens” than those used in an ABSSSI clinical trial. To fill this void, the Infectious Diseases Society of America issued guidelines in June 2012 that provide detailed recommendations for the diagnosis, surgical treatment, and antibiotic drug treatment of patients with DFI.

Contributing to the complex nature of ABSSSIs is the frequent and increasing incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) as a causative pathogen, particularly community-acquired MRSA with enhanced virulence. Recent surveillance studies indicate that MRSA was the causative pathogen in 29% to 76% of SSSIs and in 10% to 30% of DFIs. Approximately half of the MRSA isolates are USA300, the predominant strain causing community-associated ABSSSIs. Factors that increase the risk of MRSA in DFIs include a history of MRSA infection, nasal carriage of MRSA, a history of long-term or inappropriate use of antibiotic agents, previous hospitalization, long duration of a foot wound, and the presence of osteomyelitis. Thus, empirical coverage of MRSA in DFI according to the current guidelines should include the following situations: a history of MRSA infection or colonization within 1 year, a reasonable probability of MRSA infection (30%–50% local prevalence for MRSA), and MRSA severe enough that it would be prudent to empirically cover it.

Although MRSA is a common cause of DFI, clinical data on the treatment of MRSA in the diabetic foot are sparse. Data on antibiotic drug treatment of patients with DFI originate from subgroup analyses performed in clinical cSSSI studies. In those studies, often the number of MRSA infections is limited and outcomes are not stratified by MRSA owing to the low number of patients (Table 1).

Further evidence indicating the need for a better understanding of the efficacy of antibiotic drug therapy in DFI caused by MRSA comes from reports of decreased susceptibility of MRSA, and *S. aureus* in general, to vancomycin. Vancomycin has been the standard treatment for a variety of infections caused by MRSA. However, a recent meta-analysis of 14 clinical trials comparing six antibiotic agents showed that the success rate (clinical/microbiological) for vancomycin for MRSA cSSSI was 75%, which was lower than the success rates of four of the other antibiotic drugs analyzed, including daptomycin. The clinical use of vancomycin may also be problematic owing to variable target trough concentrations with the need for therapeutic drug monitoring, especially in patients with MRSA infection with reduced vancomycin susceptibility or a high incidence of renal insufficiency, as commonly seen in diabetic patients.

A retrospective review was conducted to assess the outcomes and safety of daptomycin in patients with a DFI caused by MRSA in the United States and worldwide from two large registries between 2006 and 2009. The cohort reported herein is one of the largest to date of patients with a DFI caused by MRSA.

**Methods**

**Data Source**

Real-world experience with daptomycin was tracked using the Cubicin Outcomes Registry and Experience (CORE) and the European CORE (EU-CORE) programs between 2006 and 2009. The CORE in the United States and the EU-CORE in the European Union, Latin America, India, and Russia are multicenter, retrospective, noncomparative, observational studies. Data from approximately 2,000 patients per year from the United States, the European Union, and other countries who received one or more doses of daptomycin for a gram-positive infection outside of a clinical trial were retrospectively collected via medical record review by a trained health-care provider using a standardized case report form. The protocol was approved by the health authority and the institutional review board or ethics committee, as required, in each country.

**Patients**

Patients included in this report were those with a diagnosis of DFI and documented MRSA infection with or without osteomyelitis. Outcomes were assessed at the end of daptomycin therapy. The evaluable population included all of the patients with an assessed outcome of cure, improvement, or failure, defined as follows: cure—clinical signs and symptoms are resolved and no additional antibiotic drug therapy is necessary, or the infection cleared with a negative culture reported at the end of therapy; improved—partial resolution of clinical signs and symptoms and additional antibiotic drug therapy necessary at the end of therapy; and failure—inadequate response to therapy; resistant, worsening, or new/recurrent signs and symptoms; a
need for a change in antibiotic drug therapy; or a positive culture result reported at the end of therapy. Success was defined as the sum of those cured and improved among evaluable patients. Patients were deemed nonevaluable if the reviewing investigator could not determine response at the end of therapy because the patient’s medical record did not contain adequate information. All of the evaluable and nonevaluable patients were included in the safety population.

**Data Collection**

Demographic data collected during medical record review included patient-specific characteristics (age, sex, and weight), patient location 48 hours before initiation of daptomycin therapy (community, hospital, nursing home/extended care facility, or other), concurrent comorbidities and disease states, renal function by estimated creatinine clearance, previous and concomitant antibiotic drug therapy, inpatient and outpatient use of daptomycin, duration of daptomycin treatment, location where daptomycin was received (intensive care unit/critical care unit was used as an indicator of illness severity), and surgical intervention. Microbiological and clinical data were recorded as well. Microbiological data consisted of culture and susceptibility results obtained before or shortly after initiation of daptomycin therapy. The investigator identified the causative pathogen(s) based on laboratory data. This report focuses on MRSA exclusively. Clinical data included the dose, dosing interval, and duration of daptomycin therapy for each patient, as well as the time (number of days) taken for each patient to demonstrate clinical response based on signs/symptoms or culture results at the discretion of the investigator.

Adverse events (AEs) throughout the daptomycin treatment period and 30 days after the last dose of daptomycin, changes in physical findings, clinical signs and symptoms, and laboratory values consistent with serious and nonserious AEs were documented. The definition of a serious AE was any of the following: death, life-threatening event, disability/incapacity, requiring hospitalization, congenital anomaly/birth defect, or an important medical event. The relationship to daptomycin use (ie, not related, possibly related), the action taken with respect to daptomycin therapy (ie, none, stopped permanently, dose reduced, stopped temporarily), and the outcome (resolved, resolved with residual effects, death, ongoing, unknown) were also collected.

**Results**

**Demographics**

A total of 79 patients in the CORE and EU-CORE registries were identified as having a diagnosis of MRSA DFI and composed the safety population. Seventy-four patients (93.7%) were evaluable and composed the efficacy population. Five patients were nonevaluable for outcome: two were lost to follow-up, one had an AE, and two for unreported reasons. Most of the patients (66 of 74, 89.2%) were from Western European countries. Patient demographics are summarized in Table 2. Most patients were male (74.3%) and were aged 51 to 80 years (83.8%). More than 30% of the patients had a history of reduced renal function; 50.0% were in the hospital 48 hours before initiation of daptomycin treatment. Most patients had a diagnosis of hypertension (63.5%), and almost half had peripheral arterial disease (PAD) (criteria used for diagnosis not collected). Concomitant infections due to MRSA included bacteremia in six of 74 patients (8.1%) and osteomyelitis in two of 74 patients (2.7%). Surgical intervention was undertaken in 67 of 74 patients (90.5%). Of these, 32 patients had an amputation while receiving daptomycin therapy; however, data on the extent of amputation were not collected. In the remaining 35 patients, there were 34 tissue debridements, six incisions and drainages, one bone debridement, and eight unspecified surgical procedures.

**Daptomycin Dosing**

The median initial and final doses of daptomycin were both 4.8 mg/kg (range, 3–9 mg/kg). Overall, 69 patients (93.2%) were initially treated with at least 4 mg/kg of daptomycin, 22 (29.7%) with at least 6 mg/kg, and 1 (1.4%) with at least 8 mg/kg. The final daptomycin dose was unchanged from the initial dose except in one patient whose dose was decreased from 5.4 to 3.8 mg/kg for an unknown reason. Most patients (63 of 74, 85.1%) were initially treated with daptomycin once every 24 hours. The remaining 11 patients (14.9%) received daptomycin every 48 hours, as recommended for patients with creatinine clearance less than 30 mL/min. The dosing interval of the final daptomycin dose was unchanged from the initial dosing interval in all but three patients. In these three patients, the dosing interval was adapted based on their renal function to match the recommendations provided on the label. Most patients (70 of 74, 94.6%) received a
portion of daptomycin therapy as inpatients; the median daptomycin inpatient treatment duration was 14.0 days (range, 1–59 days). Ten patients (13.5%) received daptomycin as outpatients for a median of 14.5 days (range, 4–42 days). The median total duration of daptomycin therapy was 15.0 days (range, 5–59 days).

### Previous and Concomitant Antibiotic Drug Therapy

Most patients received daptomycin as first-line therapy (43 of 74, 58.1%); the remaining patients received daptomycin after receiving one or more other antibiotic agents (31 of 74, 41.9%) (Table 3). Seventeen of these 31 patients (54.8%) were treated with an antibiotic drug that did not have activity against MRSA. Therefore, overall, 77.0% of patients (57 of 74) received initial therapy with activity against MRSA. Vancomycin was the antibiotic used in 9 of 31 patients (29.0%). Of these nine patients, three were reported as vancomycin failures. Although the number of patients treated as outpatients was small, the previous use of antibiotic agents was similar regardless of treatment setting. The most common reasons provided for switching to daptomycin therapy were failure (11 of 31, 35.5%), a resistant gram-positive pathogen (7 of 31, 22.6%), and a narrowed antibiotic spectrum (6 of 31, 19.4%).

Most of the patients (42 of 74, 56.8%) received concomitant antibiotic drugs with daptomycin; the most frequent were fluoroquinolones and carbapenem (Table 3). Forty-one patients had a mixed infection with MRSA and another pathogen identified, with a gram-negative bacillus (genus and species were not collected) being the most common (Table 4).

### Outcomes

In the 74 patients who compose the efficacy population, the overall clinical success rate was 89.2%, with 48.6% cured (n = 36) and 40.5%
improved \((n = 30)\). Treatment failure was the outcome for eight patients \((10.8\%)\). In the subset of patients with PAD, the success rate \((35 of 36, 97.2\%)\) was numerically higher than in those without PAD \((31 of 38, 81.6\%)\) \((P = .06)\). More patients with PAD had an amputation; however, even after excluding amputations, success rates continued to be higher for patients with PAD \((18 of 18, 100\%)\) compared with those without PAD \((18 of 24, 75.0\%)\).

Daptomycin therapy was successful \((cured + improved)\) in five of six patients \((83.3\%)\) with bacteremia and in two of two patients \((100\%)\) with osteomyelitis. One of the two patients with osteomyelitis received daptomycin for 18 days with a surgical amputation and the other for 55 days with tissue debridement. Follow-up outcomes after the end of therapy were not collected. Success with daptomycin therapy was statistically significantly higher in patients who had surgery \((62 of 67, 92.5\%)\) compared with those who did not \((4 of 7, 57.1\%)\) \((P = .02 by the Fisher exact test)\). Patients whose initial therapy was daptomycin had a numerically higher success rate \((36 of 38, 94.7\%)\) compared with those who switched to daptomycin \((25 of 31, 80.6\%)\) \((P = .13)\); five patients had an unknown antibiotic drug therapy history.

For the 49 patients with available data, the median time to response was 12 days \((range, 1–64 days)\) and was not influenced by the presence of PAD. The reported time to response was shorter in US patients \((3 days)\) than in patients from other countries \((13.5 days)\) \((P = .08)\). However, this difference did not lead to different treatment durations \((median and interquartile range)\) by region \((United States: 11.5 days and 8, 21 days; and non–United States: 15 days and 10, 21 days; \(P = .5)\). The factors contributing to this difference were not collected, but may represent different approaches or opportunities to document response.

### Safety

Eleven of 79 patients \((13.9\%)\) had a total of 14 AEs, with five patients experiencing at least one serious AE. Although there were no creatine phosphokinase elevations reported as an AE, data on creatine phosphokinase values during therapy were obtained in 36 patients \((45.6\%)\), and one patient \((1.3\%)\) had a value at least ten times the upper limit of normal; all of the other patients had maximum values less than five times the upper limit of normal. There were six AEs in five patients \((6.3\%)\) that were classified as serious, and one of these was possibly related to

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**Table 1. extended**

<table>
<thead>
<tr>
<th></th>
<th>Esposito et al(^\text{12})</th>
<th>Itani et al(^\text{13})</th>
<th>Lipsky and Stoutenburgh(^\text{14})</th>
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<td><strong>271 (ITT)</strong></td>
<td>(1,052) (ITT)</td>
<td>(103)</td>
<td></td>
</tr>
<tr>
<td>83</td>
<td>(640^a)</td>
<td>(55^b)</td>
<td></td>
</tr>
<tr>
<td>271</td>
<td>(106)</td>
<td>(103)</td>
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<td>NR</td>
<td>(10)</td>
<td></td>
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<td>Multicenter, observational, consecutive patients</td>
<td>Prospective, randomized, open label, comparator controlled, multicenter, phase 4</td>
<td>Prospective, randomized, investigator blinded, comparator controlled, multicenter, phase 3</td>
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<td>At the investigator’s discretion; most common: piperacillin/tazobactam, levofloxacin, amoxicillin/clavulanate, ciprofloxacin, teicoplanin, ceftriaxone, clindamycin, ampicillin/sublactam, co-trimoxazole</td>
<td>Linezolid, 600 mg IV/PO q12h (\times 7–14) d versus Vancomycin, 15 mg/kg q12h (\times 7–14) d Aztreonam (or other antibiotic drugs inactive against gram-positive/MRSA) + metronidazole were permitted</td>
<td>Daptomycin, 4 mg/kg IV qd (\times 7–14) d versus Vancomycin, 1 g q12h IV, or semisynthetic penicillin, 4–12 g/d (\times 7–14) d</td>
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<tr>
<td>93.4(^c)</td>
<td>68.3% for all of the per-protocol participants</td>
<td>MSSA: 79% ((15 of 19)) versus 79% ((15 of 19)) MRSA: 0% ((0 of 1)) versus 67% ((6 of 9))</td>
<td>MSSA: 63% ((12 of 19)) versus 68% ((13 of 19)) MRSA: 0% ((0 of 1)) versus 33% ((3 of 9))</td>
</tr>
<tr>
<td>NR</td>
<td>85.4% versus 68.8% for per-protocol participants ((N = 461))</td>
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</table>

\[^a\] For the 49 patients with available data, the median time to response was 12 days \((range, 1–64 days)\) and was not influenced by the presence of PAD. The reported time to response was shorter in US patients \((3 days)\) than in patients from other countries \((13.5 days)\) \((P = .08)\). However, this difference did not lead to different treatment durations \((median and interquartile range)\) by region \((United States: 11.5 days and 8, 21 days; and non–United States: 15 days and 10, 21 days; \(P = .5)\). The factors contributing to this difference were not collected, but may represent different approaches or opportunities to document response.

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An AE judged by the investigator to be possibly related to daptomycin therapy occurred in two patients (2.5%); daptomycin therapy was discontinued in both patients. In one of the two patients, a rash occurred that resolved with treatment. The second patient was a 68-year-old man weighing 78 kg with underlying diabetes, hypertension, cardiovascular disease, and chronic obstructive pulmonary disease; he received daptomycin for 15 days, initially at 6.4 mg/kg every 48 hours (estimated creatinine clearance, ∼30 mL/min) and then switched on an unknown day to 12.8 mg/kg (approximately 1 g) every 12 hours (renal function unreported). This patient had a serious AE, sudden cardiac death, which occurred 13 days after completing daptomycin therapy.

Discussion

Methicillin-resistant *S aureus* is a common pathogen in DFIs, and because of the increasing prevalence of community-acquired MRSA with enhanced virulence, anti-MRSA therapy has become an important treatment consideration. In this report of patients with documented MRSA DFIs, most patients received anti-MRSA therapy initially with either daptomycin (43 of 74; 58.1%) or another antibiotic agent (14 of 74; 18.9%). The remainder, 23%, did not receive appropriate first-line antibiotic drug therapy presumably because MRSA coverage was not thought to be necessary. *Staphylococcus aureus*, methicillin-sensitive *S aureus*, and MRSA are the most common pathogens causing DFI worldwide.

Therefore, it may be advantageous to start treatment with antibiotic drugs that are active...
against both methicillin-sensitive \textit{S aureus} and MRSA, especially in countries where MRSA is common. It has been demonstrated that early use of anti-MRSA treatment in cSSSIs in settings with elevated MRSA rates is associated with lower in-hospital mortality rates and significantly shorter hospital stays and lower total treatment costs.\(^{25}\)

All of these factors indicate that the early use of a highly potent antibiotic agent active against a broad range of cSSSI pathogens, including methicillin-sensitive \textit{S aureus} and MRSA, is a reasonable treatment strategy.

Given the increased prevalence of MRSA in DFI, treatment guidelines from multiple organizations have recommended empirical coverage of MRSA in at-risk patients. The 2012 Infectious Diseases Society of America guidelines recommend antibiotic drug selection based on 1) clinical evidence of infection, 2) risk of MRSA, 3) recent antibiotic drug use, 4) risk factors for \textit{Pseudomonas} infection, and 5) infection severity.\(^{5}\) For moderate or severe DFI with MRSA as the probable pathogen, daptomycin, linezolid, and vancomycin are recommended as empirical therapy. The Infectious Diseases Society of America guidelines note that 1) daptomycin can be dosed once daily but requires serial monitoring of the creatine phosphokinase level; 2) unlike the other MRSA active agents, linezolid is Food and Drug Administration indicated for the treatment of DFI, partially due to DFI being excluded by the Food and Drug Administration from its 2010 guidance for industry regarding the clinical development of drugs for the treatment of ABSSSIs.\(^{4}\) To our knowledge, this cohort of 74 patients is the largest group of patients reported with DFI caused by MRSA (Table 1).

The high clinical success rate of 89.2\% observed in this analysis is noteworthy for several reasons. This patient population represents contemporary practice, including patients with risk factors for DFI,\(^{5,26,27}\) Most of the patients in this analysis were older than 50 years and had hypertension and PAD. Peripheral arterial disease is a known risk factor for infection through its effects on wound healing.\(^{5}\) The higher success rate observed in patients with PAD compared with those without PAD, which was seen in US and non-US countries, in the present study suggests that daptomycin reaches the site of infection at adequate levels. Good tissue penetration of daptomycin is also supported by the study by

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Frequency (No.)</th>
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<tbody>
<tr>
<td>Gram-negative bacilli</td>
<td>17</td>
</tr>
<tr>
<td>\textit{Staphylococcus} spp, coagulase negative</td>
<td>6</td>
</tr>
<tr>
<td>\textit{Corynebacterium} spp</td>
<td>3</td>
</tr>
<tr>
<td>\textit{Enterococcus faecalis}, vancomycin sensitive</td>
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</tr>
<tr>
<td>\textit{Enterococcus} spp</td>
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</tr>
<tr>
<td>\textit{Peptostreptococcus} spp</td>
<td>1</td>
</tr>
<tr>
<td>\textit{Staphylococcus} spp, methicillin resistant</td>
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</tr>
<tr>
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<tr>
<td>\textit{Streptococcus pyogenes}</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
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when used for more than 2 weeks; and 3) vancomycin minimum inhibitory concentrations are gradually increasing for MRSA.\(^{5,15-17}\) Similarly, the Spanish guidelines\(^{24}\) recommend daptomycin as one of the treatments of choice, although in cases of ischemia with a risk of bacteremia, daptomycin is recommended at doses of 8 to 10 mg/kg owing to its concentration-dependent bactericidal activity even in the presence of biofilms and its lack of nephrotoxicity.

This analysis of the CORE and EU-CORE registries provides a real-world assessment of the effectiveness and safety of daptomycin in the treatment of patients with DFIs. Real-world assessments are needed, especially with the lack of randomized controlled antibiotic drug trials for DFI, partially due to DFI being excluded by the Food and Drug Administration from its 2010 guidance for industry regarding the clinical development of drugs for the treatment of ABSSSIs.\(^{4}\) To our knowledge, this cohort of 74 patients is the largest group of patients reported with DFI caused by MRSA (Table 1).

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Kim et al\textsuperscript{28} in which tissue penetration was evaluated using in vivo microdialysis in diabetic patients and healthy volunteers (n = 6 each) for thigh tissue penetration. The degree of penetration as measured by the mean ± SD ratio of the area under the free drug concentration-time curve for tissue to that of plasma was 0.93 ± 0.61 for diabetic patients and 0.74 ± 0.09 for healthy volunteers (P = .46).\textsuperscript{28} The success rate in those whose initial therapy was daptomycin was high (42 of 44, 95.5\%). Even those who switched to daptomycin had a good success rate (25 of 31, 80.6\%), particularly when one considers that most previous antibiotic drugs were not directed against MRSA and this group of patients may have had a delay in time to appropriate therapy. The success rate of daptomycin therapy in patients who failed previous antibiotic drug therapy was 72.7\% (8 of 11) despite the delay in initiating daptomycin therapy.

Daptomycin has demonstrated good efficacy compared with vancomycin in DFIs.\textsuperscript{14} In the post hoc subgroup analysis of DFI from the two registrational cSSSI trials, there were 103 clinically evaluable patients with DFI. Overall, the clinical success rates were 66\% for daptomycin and 70\% for vancomycin or penicillinase-resistant penicillin (95\% confidence interval, −14.4 to 21.8). The small number of patients with MRSA DFI (n = 10) precludes comparison with the present analysis. Also, the outcomes are typically lower owing to strict and extensive criteria leading to an assessment of failure.

Daptomycin therapy was observed to be generally well tolerated in the present analysis, with AEs similar to those reported in phase 3 cSSSI trials of daptomycin.\textsuperscript{20} Of the 14 AEs observed in the present analysis, only two were judged by the investigator to be possibly related to daptomycin use, and no AEs related to creatine phosphokinase elevations were reported. The patient with the rash had complete resolution after discontinuation of daptomycin therapy and the provision of supportive treatment. There were insufficient data collected to further describe the patient who experienced sudden cardiac death approximately 2 weeks after completing high-dose daptomycin therapy.

Although the registry nature of the CORE and EU-CORE programs provides real-world data, it does not allow for a determination of, or account for, variations in practice among attending physicians. Such differences are suggested by the small number of patients treated with outpatient therapy and the longer time to response in non-US countries compared with that in the United States. This latter difference may also reflect variations in criteria for assessing response or local approaches to patient management. The difference in the proportion of patients treated in the outpatient setting may reflect a preference for longer inpatient treatment in the European countries. Also, during this time frame of 2007 to 2009, there was a relatively smaller proportion and number of patients with DFIs from the US due to an expansion of daptomycin use for other infection types and pathogens.

The 2012 Infectious Diseases Society of America guidelines suggest continuing antibiotic drug therapy until, but not beyond, resolution of findings of infection, but not through complete healing of the wound. For moderate-to-severe infections, an initial antibiotic drug course of 2 to 3 weeks is suggested.\textsuperscript{5} The treatment duration in this study was not different by region but was consistent with the guidelines. Another limitation of a registry-based analysis is the retrospective, noncomparative, unblinded, and nonrandomized nature of the data. The medical record review nature of this analysis was also limited by an inability to characterize the type and extent of amputation. The relatively high incidence of amputation may be an indication of the severity of illness with these patients but may also be an indicator that earlier use of antibiotic drugs with activity against MRSA, including daptomycin, combined with optimized wound care are needed to improve outcomes. The data also could not be queried as to the extent of PAD; however, the higher success rate in those with versus those without PAD may minimize this latter limitation.

In summary, the results of this analysis using real-world data from patients with MRSA DFIs show daptomycin to have good clinical outcomes in these difficult-to-treat infections with a favorable safety profile. The lack of empirical MRSA coverage, 23\% in this cohort, could be improved by appropriately choosing first-line antibiotic drug therapy for DFI in countries where MRSA is common.

**Acknowledgment:** The contributions of the CORE and EU-CORE investigators and the institutions from which the data were collected.

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**Conflict of Interest:** Dr. Quast has received lecture fees from Eli Lilly & Co and Bristol-Myers

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Squibb. Dr. Crompton, Ms. Yoon, Dr. Lamp, and Dr. Culshaw are employees of Cubist Pharmaceuticals Inc. Dr. Chaves is an employee of Novartis Pharma AG. Dr. Joseph was not involved in the decision to publish or in the acceptance for publication process.

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