Daptomycin for Complicated Skin Infections: A Randomized Trial

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abstract

BACKGROUND: Complicated skin and skin structure infections (cSSSI) are common in children. Due to safety and resistance issues with recommended agents, new treatment options would be advantageous.

METHODS: Multicenter, evaluator-blinded clinical trial. Patients 1 to 17 years old with cSSSI caused by Gram-positive pathogens were randomized 2:1 to intravenous daptomycin or standard-of-care (SOC) treatment for ≤14 days. Daptomycin was administered once daily with dosing by patient age: 12 to 17 years, 5 mg/kg; 7 to 11 years, 7 mg/kg; 2 to 6 years, 9 mg/kg; 12 to 23 months, 10 mg/kg. The primary objective was to evaluate daptomycin safety. The secondary objective was to assess the efficacy of daptomycin compared with SOC. The intent-to-treat (ITT) population consisted of all randomized patients with any dose of study drug.

RESULTS: The ITT population comprised 257 daptomycin and 132 SOC patients (primarily clindamycin or vancomycin); 35% had confirmed methicillin-resistant *Staphylococcus aureus*. The most common adverse events were diarrhea (7% daptomycin, 5% SOC) and increased creatine phosphokinase (6% daptomycin, 5% SOC). The proportions of safety population patients with treatment-related adverse events were similar between the daptomycin (14%) and SOC (17%) groups. Clinical success rates (blinded evaluator–assessed complete/partial resolution of cSSSI signs and symptoms 7–14 days after end-of-treatment) in the ITT population were also similar for the daptomycin (91%) and SOC groups.

CONCLUSIONS: Once-daily daptomycin was well tolerated, with safety and efficacy comparable to SOC in children/adolescents with cSSSI caused by Gram-positive pathogens, including community-acquired methicillin-resistant *S aureus*.

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Dr Bradley contributed to the study design, enrolled patients into the clinical trial, was involved in interpretation of the data, was involved in developing the first draft of this manuscript, and revised subsequent drafts based on coauthor comments; Dr Glasser was involved in data analysis, was involved in interpretation of the data, was involved in developing the first draft of the manuscript, and revised subsequent drafts based on coauthor comments; Dr Patino and Ms Yoon contributed to study design, were involved in data analysis, and were involved in interpretation of the data; Drs Arietta and Arnold contributed to study design and enrolled

WHAT'S KNOWN ON THIS SUBJECT: Complicated skin and skin structure infections (cSSSI) caused by community-acquired methicillin-resistant *Staphylococcus aureus* are common in children. Available treatments (eg, vancomycin, clindamycin, and linezolid) can have important drawbacks, stressing the need for safer, uniformly active, and effective alternatives.

WHAT THIS STUDY ADDS: This randomized, controlled trial evaluating daptomycin for cSSSI in children documents that daptomycin was well tolerated in pediatric patients with Gram-positive cSSSI, with efficacy comparable to standard-of-care therapy (the trial was not powered to confirm noninferiority).

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Complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus*, including community-acquired methicillin-resistant *S aureus* (CA-MRSA), are common in children.[1–4] Many such infections are sufficiently severe that hospitalization and parenteral therapy are considered necessary. Guidelines recommend vancomycin as parenteral therapy for invasive CA-MRSA infections in children, with clindamycin as an alternative.[5–7] Vancomycin, particularly at the higher doses recommended for treating CA-MRSA, requires renal function and vancomycin serum concentration monitoring.[5,8,9] Clindamycin is well tolerated, but where resistance rates exceed 10% to 15%, treatment failure risk limits empiric use.[5–7,9] Linezolid is another alternative; however, it carries concerns about myelosuppression and neurotoxicity, restricting routine usage.[10–13] Alternative safe, effective, evidence-based therapies are therefore needed.

Daptomycin is a parenteral lipopeptide antibiotic approved for treatment of cSSSI, and Gram-positive bacteremia, in adults. It is active against all clinically significant Gram-positive pathogens, including MRSA, methicillin-susceptible *S aureus* (MSSA), other staphylococci, streptococci, and enterococci (including vancomycin-resistant strains).[14] Clinical trials have established the safety and efficacy of daptomycin for treating cSSSI in adults.[15–18] Pharmacokinetic studies demonstrated that children require higher daptomycin doses (varying by age) to achieve steady-state exposure comparable to adult plasma levels associated with treatment success.[19–21] Substantial clinical and safety data regarding daptomycin use in pediatric patients are still lacking. This article reports a randomized controlled clinical trial comparing safety and efficacy of daptomycin versus intravenous (IV) standard-of-care (SOC) antibacterial therapy in pediatric patients with cSSSI caused by Gram-positive pathogens.

METHODS

Protocol DAP-PEDS-07-03 was an evaluator-blinded, randomized, phase 4 study at 23 children's hospitals in the United States and 7 in India between July 2008 and October 2013. The study was conducted in accordance with the principles of Good Clinical Practice and approved by the appropriate institutional review boards and regulatory agencies. Written parental (or alternative legal representative) consent was required for all patients before undergoing study-related procedures, as was child assent, if appropriate.

Patients

Eligible patients were between 1 and 17 years old and had cSSSI (deep soft tissue infections, infections requiring significant surgical intervention, or skin infections in patients with significant underlying conditions likely to complicate treatment response) known or suspected to be caused by Gram-positive bacteria and thought to require IV antibacterial therapy. Inclusion/exclusion criteria underwent minor amendments as the study progressed to facilitate enrollment. Patients needed to have ≥3 cSSSI signs/symptoms: body temperature >37.5°C oral or >38°C rectal/forehead/aural; white blood cell count >12 000/mm^3 or ≥10% immature neutrophils; pain; tenderness to palpitation; swelling and/or induration; erythema (>1 cm beyond the edge of cSSSI); and/or purulence. Patients were excluded if they had >24 hours of systemic antibacterial therapy during the 48 hours before the first dose of the study drug, unless the causative pathogen was nonsusceptible or this previous therapy had not yielded clinical improvement. Key additional exclusion criteria were: cSSSI confirmed to involve no Gram-positive bacteria; bacteremia, pneumonia, osteomyelitis, meningitis, or endocarditis; renal insufficiency; and/or any laboratory abnormalities or clinical findings (including creatine phosphokinase [CPK] elevations, rhabdomyolysis, myositis, muscular disease or weakness, and peripheral neuropathy) with potential to increase the hypothetical risk of daptomycin toxicity[22–24] or to complicate evaluation of treatment-emergent muscle/nerve toxicity.

Study Design

Each study site designated an unblinded investigator and a blinded evaluator; the latter did not enroll patients and remained blinded throughout each treatment course. Eligible patients were randomized to receive IV treatment of ≤14 days in a 2:1 ratio (daptomycin:SOC). Randomization was implemented using a centralized, computer-generated randomization schedule, stratified by 4 separate age cohorts (12–17 years, 7–11 years, 2–6 years, and 12–23 months). These cohorts were sequentially enrolled and evaluated (with respective protocol amendments), starting with the oldest age group to ensure adequate safety evaluation before proceeding to the next-younger cohort. Daptomycin was given once daily at age-dependent doses (12–17 years, 5 mg/kg; 7–11 years, 7 mg/kg; 2–6 years, 9 mg/kg; 12–23 months, 10 mg/kg).[19–21] The SOC agent was selected before randomization by the unblinded investigator based on local treatment practice. Aztreonam and/or metronidazole as adjunctive therapy for mixed Gram-positive/Gram-negative infections were permitted at the investigator's discretion.

The blinded evaluator determined IV treatment duration and could switch to oral therapy after ≥24 hours if the pathogen was confirmed as susceptible to the oral agent (if microbiology results were available)

and there was clear improvement in cSSSI signs/symptoms. The unblinded investigator then decided on oral drug and duration. The blinded evaluator also assessed the relationship of adverse events (AEs) to the study treatment and assessed signs/symptoms of the primary cSSSI site at baseline, end-of-treatment (within 3 days after last dose of study drug [IV and oral]), and test-of-cure (7–14 days after the last dose of study drug).

Outcomes

The primary objective was to assess the safety of age-dependent doses of daptomycin in comparison with SOC. The safety population included all patients who received ≥1 dose of study medication (according to the actual treatment received) and underwent ≥1 postdose safety evaluation. AEs were monitored from the first dose to the test-of-cure visit. Physical, neurologic, and laboratory tests (including serum CPK level) were performed at predefined times throughout the study (Supplemental Table 6). In the event of clinically significant serum creatinine increases, the creatinine clearance rate was calculated; if the creatinine clearance rate was <80 mL/min per 1.73 m^2, then the patient was discontinued from IV treatment. The primary outcome measure was the percentage of patients with treatment-emergent AEs from baseline through 14 days after the last dose of study drug.

A secondary study objective was to compare the efficacy of daptomycin and SOC, but the study was neither designed nor powered to confirm noninferiority. Secondary outcome measures included (Supplemental Tables 7 and 8):

- Clinical response at end-of-treatment and test-of-cure in the intent-to-treat (ITT) population (randomized patients with any dose of study drug) and clinically evaluable (CE) population (ITT patients without predefined confounding factors, ≥3 days of study therapy, and evaluable at test-of-cure);
- Microbiologic response at end-of-treatment and test-of-cure in the modified intent-to-treat (MITT) population (ITT patients with a confirmed Gram-positive baseline pathogen) and the microbiologically evaluable (ME) population (CE patients with a confirmed Gram-positive baseline pathogen);
- Overall therapeutic success (ie, combined clinical cure and microbiologic success at test-of-cure in the ME population).

Patients whose clinical course could not be clearly described as "improved" were classified as treatment failures; clinical failures at end-of-therapy were carried forward as failures to test-of-cure. Patients lost to follow-up or receiving <3 days of the study therapy (IV and oral combined), were classified as "unable to evaluate." Pathogen isolate susceptibility and minimum inhibition concentrations (MIC) were determined (Supplemental Table 9).

Pharmacokinetic Evaluation

The evaluation of daptomycin pharmacokinetics by age group was an additional objective (Supplemental Tables 10 and 11). The protocol was amended to use sparse pharmacokinetic sampling in the youngest cohort to mitigate pain and reduce blood draws. Pharmacokinetic data were pooled and analyzed through Phoenix WinNonlin version 6.2 (Pharsight Corporation, Mountain View, CA). The area under the plasma concentration time curve from 0 to the last sampling time point in each cohort was a secondary outcome measure.

Statistical Analysis

Data were pooled across study sites and analyzed using SAS (SAS Institute, Inc., Cary, NC). Descriptive statistics were derived for continuous and categorical variables. The study was not powered to compare safety or efficacy end points between treatment arms. The sample size was selected in collaboration with the US Food and Drug Administration to support the primary end point of safety (Supplemental Table 12). For descriptive differences in treatment success rates between study arms, normal approximation 95% confidence intervals (CIs) were constructed for the total study population and 3 older age groups and exact 95% CIs for 12–23-months-old patients.

RESULTS

Patients

The ITT population comprised 257 patients randomized to daptomycin and 132 randomized to SOC (Fig 1). Demographics and baseline characteristics were balanced between treatment groups; most patients presented with a major abscess or complicated cellulitis (Table 1). Similar incidences of baseline symptoms, including localized pain, swelling, and redness, were reported across all age groups in both treatment arms. Approximately 80% of patients in each arm had a Gram-positive baseline pathogen confirmed by culture (Table 1). *S aureus* was predominant, and >50% (145/280) of all baseline staphylococcal isolates were methicillin-resistant. All baseline isolates were daptomycin susceptible (MIC_{50}, 0.25 μg/mL; MIC_{90}, 0.5 μg/mL; MIC range for staphylococci and streptococci, 0.03–1 μg/mL). In the SOC arm, 13 of the 133 patients (10%) had baseline isolates nonsusceptible to the first-line parenteral agent administered (11 isolates to clindamycin, 1 isolate to cefazolin, and 1 isolate to amoxicillin/clavulanate) (Supplemental Table 13). Among SOC patients with MRSA, 29 of 46 (63%) received initial IV treatment with clindamycin and 12 of 46 (26%)

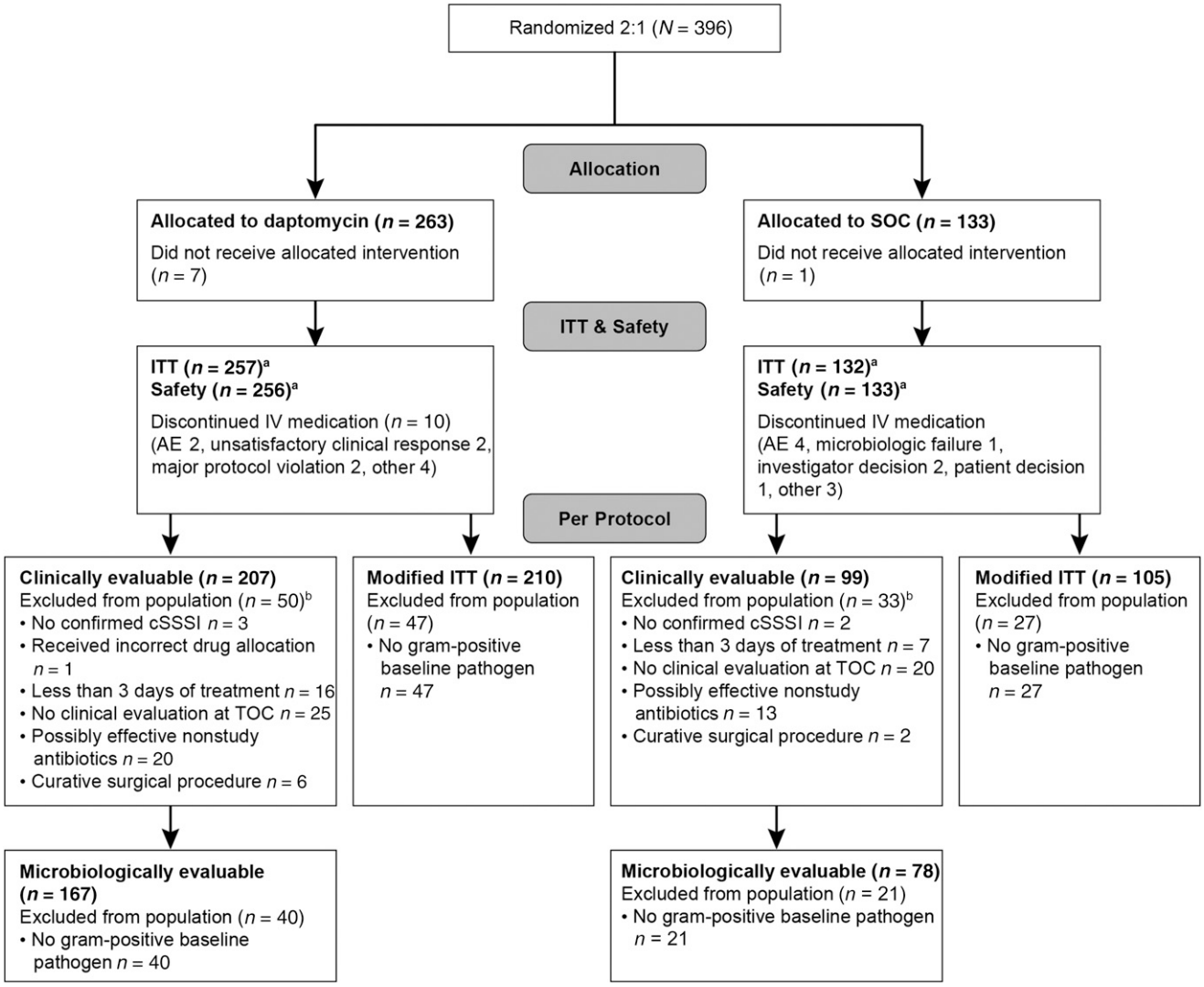

FIGURE 1

Patient disposition. [a]One patient in the 12- to 17-year-old age group was randomized to daptomycin, but was treated with SOC (IV treatment was completed). [b]Patients could have had more than 1 reason for exclusion from the clinically evaluable population. Per study protocol, this patient was included in the SOC safety population (for purposes of all safety evaluations), included in the daptomycin ITT population, and excluded from the CE population. TOC, test-of-cure.

with vancomycin. Of 472 unique isolates, 66 (14%) were clindamycin nonsuspectible, and an additional 17 (4%) showed inducible clindamycin resistance.

About 95% of ITT patients completed IV study drug treatment (Fig 1). The most commonly used IV therapies in the SOC arm were clindamycin (50%; 67/133) and vancomycin (42%; 56/133). A post-hoc analysis showed that the duration of IV therapy was shorter with daptomycin: 47% (120/256) of daptomycin patients received <3 days of IV therapy, compared with 35% (47/133) of SOC patients (Fig 2) (95% CI for the difference, –1.4% to 21.7%). Five SOC patients, but no daptomycin patients, required change to an alternative IV drug. Most patients (95% daptomycin, 94% SOC) were switched to oral therapy, most commonly clindamycin (99/244 [39%] in the daptomycin arm and 47/125 [35%] in the SOC arm). Durations of oral treatment (median, 9 days; range, 2–33 days) and total treatment (median, 12 days; range, 1–35 days) were similar in both arms (Supplemental Table 14).

Both treatment arms had comparable proportions of patients within the ITT, MITT, CE, and ME analysis populations (Fig 1). The reasons for exclusion from the CE population were also similar across treatment and age groups. The lack of clinical evaluation at test-of-cure (10% daptomycin; 15% SOC) and the receipt of possibly effective nonstudy antibiotics (8% daptomycin; 10% SOC) accounted for the majority of exclusions from the CE population (Supplemental Table 15).

TABLE 1 Demographic and Baseline Clinical Characteristics of the ITT Population

Characteristic	Daptomycin ($N = 257$), n (%)	SOC ($N = 132$), n (%)
Sex		
Boy	131 (51.0)	70 (53.0)
Girl	126 (49.0)	62 (47.0)
Race		
White	104 (40.5)	61 (46.2)
Asian	83 (32.3)	42 (31.8)
Black or African American	65 (25.3)	25 (18.9)
Other	5 (1.9)	4 (3.0)
Primary diagnosis		
Major abscess[a]	136 (52.9)	72 (54.5)
Complicated cellulitis[b]	95 (37.0)	49 (37.1)
Wound infection	21 (8.2)	9 (6.8)
Other	5 (1.9)	2 (1.5)
Gram-positive baseline pathogen documented[c]	210 (81.7)	105 (79.5)
MRSA	94 (44.8)	44 (41.9)
MSSA	78 (37.1)	41 (39.0)
Streptococcus pyogenes	19 (9.0)	7 (6.7)
Other[d]	6 (2.9)	4 (3.8)
Polymicrobial Gram-positive	13 (6.2)	9 (8.6)
Gram-negative baseline pathogen documented	10 (3.9)	3 (2.3)

[a] Defined as: abscess involving deep soft tissue and/or requiring significant surgical intervention.
[b] Defined as: cellulitis involving deep soft tissue and/or requiring significant surgical intervention.
[c] The remaining patients either had only Gram-negative pathogens or no pathogens isolated at baseline.
[d] Either *Staphylococcus* spp, *Streptococcus* spp, or *Enterococcus faecalis*.

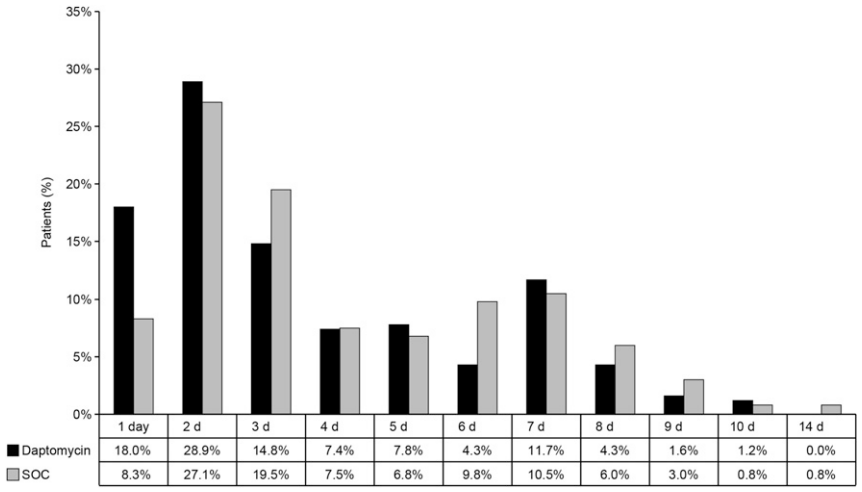

FIGURE 2
Duration of IV study drug administration (measured in days) in the daptomycin and SOC arms, based on the safety population.

Safety and Tolerability

The frequency and distribution of treatment-emergent AEs (TEAEs) were similar between the daptomycin and SOC arms. The most commonly reported TEAEs were diarrhea and increased blood CPK in both groups and fever in the daptomycin group (Tables 2 and 3); no patients experienced neuropathy. Most TEAEs were mild in intensity and were considered unrelated to the study medication by the blinded evaluator; 3% of daptomycin and 5% of SOC patients discontinued treatment due to an AE. Drug-related TEAEs were reported for 14% of daptomycin-treated and 17% of SOC-treated patients.

The frequency and distribution of serious TEAEs were also similar across treatment arms (Supplemental Table 16). In the daptomycin arm, 9 serious TEAEs occurred in 6 patients: pyrexia, abscess, and wound drainage (in 1 patient); chest pain and myopathy (in 1 patient); and pyrexia, subcutaneous abscess, increased blood CPK, and status asthmaticus (in 1 patient each). Bacteremia, osteomyelitis, and toxic shock syndrome (in 1 patient each) were the serious TEAEs in the SOC arm.

A total of 6 of 256 (2%) daptomycin-treated and 1 of 133 (1%) SOC-treated patients experienced musculoskeletal/connective tissue disorders (Supplemental Table 17); none were considered treatment-related and all but 1 were mild or moderate in severity. The only severe musculoskeletal TEAE (in a 15 year-old boy who received 2 daptomycin doses and 5 days of oral clindamycin) was myopathy 56 days after the last daptomycin dose; this TEAE was considered serious, but unlikely to be related to treatment. Increased blood CPK was reported as a TEAE in 14 of the 256 (6%) daptomycin-treated and 7 of the 133 (5%) SOC-treated patients. In patients with respective normal/low baseline values, elevated blood urea nitrogen (17/226 [8%] daptomycin, 8/112 [7%] SOC) and creatinine (5/240 [2%] daptomycin and 2/124 [2%] SOC) also occurred with similar frequency in both arms; no patients discontinued treatment due to abnormal renal function tests.

Efficacy

The clinical, microbiologic, and overall response rates are shown in Table 4. At test-of-cure in the ITT population, blinded investigator–assessed clinical success rates were similar between the daptomycin (91%) and SOC (87%) patients, including patients who were switched to oral therapy (93% and 90%, respectively). Few treatment failures were observed (1 each for

the daptomycin and SOC arms). Overall therapeutic success rates were also similar for daptomycin (97%) and SOC (99%), as were clinical success rates at test-of-cure in the CE population (100% in both arms) (Table 4). The clinical success rates did not differ between treatment arms by age group; however, success rates were slightly higher in 7- to 17-year-old patients than in 1- to 6-year-old patients overall (Supplemental Table 18).

Test-of-cure microbiologic success rates in the MITT population ranged from 70% to 100% against common pathogens (Supplemental Table 19). Most microbiologic nonsuccesses were due to patients being microbiologically nonevaluable; only 2 MITT patients in the daptomycin (and none in the SOC group) were confirmed microbiological failures at test-of-cure, and both were clinical cures at test-of-cure. One patient (with cellulitis) had a superinfection, and the other was a 1-year-old patient with major abscess on his buttock/perineum/scrotum, requiring 2 drainage procedures early during hospitalization. At the end of antibiotic therapy (3 days of daptomycin; 8 days of oral cephalexin at an unstudied dose regimen of ~25 mg/kg every 12 hours), the patient was deemed "clinically improved" by the blinded evaluator, but a residual area of inflammation was appreciated. This area developed into a scrotal abscess that required renewed drainage 2 days after end-of-therapy, with cultures documenting the same pathogen (MSSA) that was isolated at baseline. At test-of-cure, this patient was deemed a clinical cure, but because the baseline pathogen was still present early on between the end-of-therapy and test-of-cure visits, he was regarded a test-of-cure microbiological failure as per the study protocol.

Pharmacokinetics

A total of 45 daptomycin patients provided ≥1 plasma sample for pharmacokinetic analysis (Table 5). The mean apparent terminal half-life ranged from 4 to 5 hours, and clearance was higher in 1- to 6-year-old patients than in 7- to 17-year-old patients.

TABLE 2 Summary of TEAEs in the Safety Population

TEAE Category	Daptomycin (N = 256), n (%)	SOC (N = 133), n (%)
At least 1 TEAE[a]	98 (38.3)	48 (36.1)
At least 1 TESAE	6 (2.3)	3 (2.3)
At least 1 drug-related TEAE[b]	35 (13.7)	22 (16.5)
TEAE by relationship to study drug[c]		
Not related	40 (15.6)	21 (15.8)
Unlikely related	23 (9.0)	5 (3.8)
Possibly related	30 (11.7)[d]	16 (12.0)[e]
Related	5 (2.0)[e]	6 (4.5)[e]
TEAE by severity[f]		
Mild	71 (27.7)	30 (22.6)
Moderate	21 (8.2)	15 (11.3)
Severe	6 (2.3)	3 (2.3)
TEAE leading to treatment discontinuation	7 (2.7)	7 (5.3)
TEAE leading to study discontinuation	1 (0.4)	1 (0.8)

TESAE, treatment-emergent serious AE.
[a] TEAE that occurred from the time of the first dose of the study drug through the last study evaluation or preexisting AEs that were aggravated in severity or frequency during the dosing period.
[b] A drug-related TEAE was an AE that was deemed by the investigator as possibly related or as related to study drug, or if the relationship was missing.
[c] Patients were only counted once for the AE with the highest relationship to the study drug.
[d] Of these possibly study drug-related TEAEs in the daptomycin arm, 1 was serious (increased blood CPK).
[e] None of these were serious.
[f] Patients were only counted once for the AE with the highest severity.

TABLE 3 AEs Occurring in ≥2% of Patients (Safety Population) in Either Treatment Arm

AE	Daptomycin (N = 256), n (%)	SOC (N = 133), n (%)
Diarrhea	18 (7.0)	7 (5.3)
Blood CPK increased	14 (5.5)	7 (5.3)
Pyrexia	10 (3.9)	4 (3.0)
Pruritus	8 (3.1)	2 (1.5)
Headache	7 (2.7)	3 (2.3)
Vomiting	7 (2.7)	1 (0.8)
Abdominal pain	5 (2.0)	0
Diaper dermatitis	2 (0.8)	3 (2.3)
Erythema	2 (0.8)	3 (2.3)
Rash	1 (0.4)	4 (3.0)
Upper respiratory tract infection	0	3 (2.3)

The study was not powered to detect statistically significant differences in AEs between the treatment arms.

DISCUSSION

This randomized, prospective, evaluator-blinded clinical trial demonstrated the safety of daptomycin compared with SOC (mainly IV vancomycin, clindamycin, and semisynthetic penicillins) for the treatment of cSSSI in pediatric patients 1 to 17 years old. Almost 400 children, ethnically and geographically diverse, with serious infections requiring hospitalization (primarily major abscesses and cellulitis) were successfully enrolled into the study. Over 40% of infections with documented Gram-positive pathogens were caused by MRSA.

In this complex population, both daptomycin treatment and SOC treatment, each followed by suitable oral therapy, were well tolerated. In adults, daptomycin has the potential to cause CPK elevations, in particular at the higher doses used to treat bacteremia.[25] In our study, increased CPK was not more frequent in daptomycin- than in SOC-treated children, suggesting there is no need

TABLE 4 Assessment of Treatment Success by Analysis Population at End-of-Therapy (Within 3 Days After the Last Dose of Study Drug) and Test-of-Cure (7–14 Days After the Last Dose of Study Drug)

Analysis Population	Daptomycin *n*/*N* (%)	SOC *n*/*N* (%)	Difference (95% CI)
ITT: clinical success rate (assessed by blinded evaluator)			
End-of-therapy	237/256 (92.6)[a]	117/130 (90.0)[b]	2.6 (−3.5 to 8.7)
Test-of-cure	233/256 (91.0)[a]	114/131 (87.0)[b]	4.0 (−2.7 to 10.7)
ITT: clinical success rate (sponsor-defined)			
Test-of-cure	227/257 (88.3)[c]	114/132 (86.4)[d]	2.0 (−5.1 to 9.1)
MITT: clinical success rate (assessed by blinded evaluator)			
End-of-therapy	194/209 (92.8)[e]	94/104 (90.4)[f]	2.4 (−4.2 to 9.1)
Test-of-cure	190/209 (90.9)[e]	91/105 (86.7)[f]	4.2 (−3.3 to 11.8)
MITT: microbiologic success rate			
Test-of-cure	190/210 (90.5)	93/105 (88.6)	1.9 (−5.4 to 9.2)
CE: clinical success rate (assessed by blinded evaluator)			
End-of-therapy	206/207 (99.5)	99/99 (100)	−0.5 (−1.4 to 0.5)
Test-of-cure	206/207 (99.5)	99/99 (100)	−0.5 (−1.4 to 0.5)
CE: clinical success rate (sponsor-defined)			
Test-of-cure	204/207 (98.6)	99/99 (100)	−1.5 (−3.2 to 0.2)
ME: clinical success rate (assessed by blinded evaluator)			
End-of-therapy	166/167 (99.4)	78/78 (100)	−0.6 (−1.8 to 0.6)
Test-of-cure	166/167 (99.4)	78/78 (100)	−0.6 (−1.8 to 0.6)
ME: overall therapeutic success rate[g]			
Test-of-cure	162/167 (97.0)	77/78 (98.7)	−1.7 (−5.3 to 1.9)

[a] The denominator represents all ITT patients with an outcome (ie, either success, failure, or indeterminate) recorded by the investigator. Among patients without clinical success, at end-of-therapy, 16 of 256 (6.3%) were lost to follow-up and 3 of 256 (1.2%) were confirmed clinical failures, whereas at test-of-cure, 22 of 256 (8.6%) were lost to follow-up and 1 of 256 (0.4%) were confirmed clinical failures.

[b] The denominator represents all ITT patients with an outcome (ie, either success, failure, or indeterminate) recorded by the investigator. Among patients without clinical success, at end-of-therapy, 11 of 130 (8.5%) were lost to follow-up and 2 of 130 (1.5%) were confirmed clinical failures, whereas at test-of-cure, 16 of 131 (12.2%) were lost to follow-up and 1 of 131 (0.8%) were confirmed clinical failures (this patient had received an empiric regimen active against the baseline pathogen).

[c] A review by a blinded study medical monitor according to predefined criteria recategorized 7 daptomycin patients from "clinical success" to "nonevaluable" or "clinical failure" (reasons: received <3 days of study therapy, $n = 3$; signs/symptoms not recorded, $n = 2$; signs/symptoms worsened between end-of-therapy and test-of-cure, $n = 1$; or primary infection site surgically removed, $n = 1$) and 1 patient from "nonevaluable" to "clinical success." The denominator represents the full ITT population.

[d] A review by a blinded study medical monitor according to predefined criteria recategorized 1 SOC patient from "clinical success" to "nonevaluable" (received <3 days of study therapy, $n = 1$) and 1 patient from "nonevaluable" to "clinical success." The denominator represents the full ITT population.

[e] The denominator represents all MITT patients with an outcome (ie, either success, failure, or indeterminate) recorded by the investigator. Among patients without clinical success, at end-of-therapy, 12 of 209 (5.7%) were lost to follow-up and 3 of 209 (1.4%) were confirmed clinical failures, whereas at test-of-cure, 18 of 209 (8.6%) were lost to follow-up and 1 of 209 (0.5%) were confirmed clinical failures.

[f] The denominator represents all MITT patients with an outcome (ie, either success, failure, or indeterminate) recorded by the investigator. Among patients without clinical success, at end-of-therapy, 10 of 104 (9.6%) were lost to follow-up, whereas at test-of-cure, 13 of 105 (12.4%) were lost to follow-up and 1 of 105 (1.0%) were confirmed clinical failures.

[g] Combined clinical success (shown separately in this table) and microbiological success (not shown).

to proactively monitor for clinical or laboratory evidence of muscle toxicity when using daptomycin in pediatric patients at the doses studied. There were no cases of renal abnormalities leading to drug discontinuation. Children <12 months were not included in our study per agreement with regulatory agencies, because a neonatal animal model had demonstrated clinical AEs on nervous and muscular systems with daptomycin, albeit without histopathological changes indicative of nerve or muscle injury.[26] In our trial, daptomycin was not associated with an increased risk of neurologic or muscular toxicity, which is in line with previous data from smaller phase 1 safety studies.[19–21] These results are also consistent with recent retrospective, multicenter, real-world studies in children, in which daptomycin doses ranging from 4 to >10 mg/kg per day were similarly not associated with any signs or symptoms of muscular or neurologic toxicity, low to no incidence of increased CPK or serum creatinine, and no indication of CPK-related AEs.[27,28]

Both treatment arms consistently showed similar treatment response rates in all analysis populations, but our study was not designed for a formal evaluation of noninferiority between the 2 arms. Due to known pharmacokinetic differences,[19–21] children received age-adjusted daptomycin doses that were greater than the standard dose for treating cSSSI in adults, but resulted in a similar daptomycin exposure. Daptomycin clearance and the volume of distribution in these children were found to increase with decreasing age, which is consistent with previous reports.[19–21] The daptomycin doses selected for each age group achieved exposures similar to those in adults and were validated as safe and effective. At test-of-cure, there were only 2 confirmed clinical failures and 2 microbiological failures. Several factors likely contributed to this low failure rate, including among patients with pathogens that were nonsusceptible to first-line therapy: curative incision and drainage procedures, successful host response to infection, and active second-line parenteral and/or oral step-down therapy. Overall, our results suggest that daptomycin represents an alternative once-daily parenteral agent for treating cSSSI in children, which parallels the current recommendations for adults.[5,6]

Daptomycin may be particularly suitable as an alternative to vancomycin for MRSA therapy, because the higher vancomycin doses recommended for treating methicillin-resistant pathogens can cause deteriorating renal function while the patient is on therapy.[5,8] Daptomycin may also represent an alternative to empiric clindamycin in settings of relatively high clindamycin resistance (for either MRSA or MSSA) and/or in children with a greater severity of

TABLE 5 Pharmacokinetic Parameters of Daptomycin

	12–17 y[a]	7–11 y[a,b]	2–6 y[c]	12–23 mo[d]
Dosing cohort information				
No. of patients included in the pharmacokinetic analyses	*N* = 6	*N* = 2	*N* = 7	*N* = 30
Once-daily dose	5 mg/kg	7 mg/kg	9 mg/kg	10 mg/kg
Infusion duration	0.5 h	0.5 h	1 h	1 h
Pharmacokinetic parameter, mean (SD)				
C_{max} (μg/mL)	62 (10)	65, 74	82 (22)	79.2
T_{max} (h)	1 (0.1)	0.3, 0.8	1 (0.4)	1.0
$t_{1/2}$ (h)[e]	5.3 (2)	5, ND	4 (0.3)	5.04
$AUC_{0-\tau}$ (μg*h/mL)[e]	387 (81)	438, ND	439 (103)	466
AUC_{0-t} (μg*h/mL)	318 (62)	314, 347	318 (69)	466
CL_{ss} (mL/kg per h)[e]	13 (3)	16, ND	21 (5)	21.5
V_{ss} (mL/kg)[e]	98 (12)	104, ND	116 (20)	159

$AUC_{0-\tau}$, area under the plasma concentration time curve during 1 dosing interval; AUC_{0-t}, area under the plasma concentration time curve from 0 to the last sampling time point; CL_{ss}, clearance at steady-state; C_{max}, maximum plasma concentration; ND, not determined; $t_{1/2}$, half-life; T_{max}, time of maximum concentration; V_{ss}, volume of distribution at steady-state.

[a] Patients in this age group underwent rich pharmacokinetic sampling on day 3 (Supplemental Table 9). Additional informed consent, separate from the main informed consent to enter the trial, was required for patients to be included in the pharmacokinetic analysis. Because this separate informed consent was infrequently granted and because a substantial number of patients received <3 days of daptomycin therapy, only a small number of children could be included in this analysis.

[b] Two patients provided plasma samples that were used to determine pharmacokinetics. The numbers provided in this column indicate individual values.

[c] Patients in this age group underwent rich pharmacokinetic sampling on either day 1, 2, or 3 (Supplemental Table 9). Additional informed consent, separate from the main informed consent to enter the trial, was required for patients to be included in the pharmacokinetic analysis. Because this separate informed consent was infrequently granted and because a substantial number of patients received <3 days of daptomycin therapy, only a small number of children could be included in this analysis.

[d] In this age group, sparse pharmacokinetic sampling (based on a predefined random sampling schedule; Supplemental Table 9) was done for all patients assigned to daptomycin who consented to participate in the study; therefore, a larger number of patients could be included in the pharmacokinetic analysis. Due to limited pharmacokinetic samples per patient, pharmacokinetic parameters were computed using the mean concentration time profile during a sampling interval and the SD was not calculated.

[e] Not all patients had this parameter determined.

illness, in whom potential resistance can limit clindamycin's utility as empirical therapy. Given the lack of resistance concerns with daptomycin, this agent may be especially valuable if the causative pathogen is not known to be susceptible. In addition, daptomycin's once-daily dosing schedule may facilitate outpatient parenteral therapy compared with vancomycin and IV clindamycin, which are dosed every 6 to 8 hours in children.[5,6] Notably, an exploratory retrospective analysis suggested that daptomycin was associated with a faster switch to oral step-down therapy than SOC; an earlier switch to oral agents may offer many practical advantages. Given that the evaluator decided on oral step-down according to protocol-defined criteria and was blinded to treatment assignment, these results suggest that more rapid clinical improvement occurred in patients receiving daptomycin. However, an adequately powered prospective, randomized controlled trial would be required to formally evaluate this hypothesis.

Our trial was conducted in accordance with US regulations requiring pharmaceutical companies to study drugs in children after approval has been granted in adults, provided that a similar disease benefiting from drug therapy also occurs in pediatric populations. These regulations also mandate that the corresponding pediatric clinical trials use safety as the primary end point.[29] Therefore, although our study also collected robust clinical and microbiologic data, it was not designed to statistically compare the efficacy of daptomycin treatment with SOC.

CONCLUSIONS

Daptomycin was well tolerated, with comparable safety and efficacy to SOC, in pediatric patients with cSSSI caused by Gram-positive pathogens; however, this trial was not powered to confirm noninferiority. There were no differences between treatment with daptomycin and SOC in abnormal laboratory parameters, including CPK and measures of renal function. Daptomycin is a suitable once-daily alternative to vancomycin or clindamycin in the pediatric setting, particularly for suspected or confirmed MRSA infections.

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ABBREVIATIONS

AE: adverse event
CA-MRSA: community-acquired methicillin-resistant *Staphylococcus aureus*
CE: clinically evaluable
CI: confidence interval
CPK: creatine phosphokinase
cSSSI: complicated skin and skin structure infection
ITT: intent-to-treat
IV: intravenous
ME: microbiologically evaluable
MIC: minimum inhibition concentration
MITT: modified intent-to-treat
MRSA: methicillin-resistant *Staphylococcus aureus*
MSSA: methicillin-susceptible *Staphylococcus aureus*
SOC: standard-of-care
TEAE: treatment-emergent adverse event

patients into the clinical trial; Drs Congeni, Daum, and Kojaoghlanian enrolled patients into the clinical trial; Ms Anastasiou was involved in data analysis; Mr Wolf was involved in interpretation of the data, was involved in developing the first draft of this manuscript, and revised subsequent drafts based on coauthor comments; Dr Bokesch contributed to study design, was involved in data analysis and interpretation of the data, was involved in developing the first draft of this manuscript, and revised subsequent drafts based on coauthor comments; and all authors critically reviewed and approved the final version of the manuscript.

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