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MAJOR ARTICLE

Daptomycin Plus Fosfomycin Versus Daptomycin Alone for Methicillin-resistant *Staphylococcus aureus* Bacteremia and Endocarditis: A Randomized Clinical Trial

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(See the Editorial Commentary by Karchmer on pages 1526–8.)

Background. We aimed to determine whether daptomycin plus fosfomycin provides higher treatment success than daptomycin alone for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and endocarditis.

Methods. A randomized (1:1) phase 3 superiority, open-label, and parallel group clinical trial of adult inpatients with MRSA bacteremia was conducted at 18 Spanish hospitals. Patients were randomly assigned to receive either 10 mg/kg of daptomycin intravenously daily plus 2 g of fosfomycin intravenously every 6 hours, or 10 mg/kg of daptomycin intravenously daily. Primary endpoint was treatment success 6 weeks after the end of therapy.

Results. Of 167 patients randomized, 155 completed the trial and were assessed for the primary endpoint. Treatment success at 6 weeks after the end of therapy was achieved in 40 of 74 patients who received daptomycin plus fosfomycin and in 34 of 81 patients who were given daptomycin alone (54.1% vs 42.0%; relative risk, 1.29 [95% confidence interval, .93–1.8]; $P = .135$). At 6 weeks, daptomycin plus fosfomycin was associated with lower microbiologic failure (0 vs 9 patients; $P = .003$) and lower complicated bacteremia (16.2% vs 32.1%; $P = .022$). Adverse events leading to treatment discontinuation occurred in 13 of 74 patients (17.6%) receiving daptomycin plus fosfomycin, and in 4 of 81 patients (4.9%) receiving daptomycin alone ($P = .018$).

Conclusions. Daptomycin plus fosfomycin provided 12% higher rate of treatment success than daptomycin alone, but this difference did not reach statistical significance. This antibiotic combination prevented microbiological failure and complicated bacteremia, but it was more often associated with adverse events.

Clinical Trials Registration. NCT01898338.

Keywords. MRSA; bacteremia; daptomycin; fosfomycin; clinical trial.

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Bacteremia due to methicillin-resistant *Staphylococcus aureus* (MRSA) is a major healthcare problem worldwide [1, 2]. Microbiological failures including persistent and recurrent infection remain a major problem in the management of patients with MRSA bacteremia and endocarditis [3]. The persistently high mortality rate in MRSA bacteremia, ranging from 13% to 30%, is a matter of concern [4–6]. A major factor contributing to these adverse outcomes is the limited efficacy of the current standard antibiotic therapy with either vancomycin or daptomycin [7].

Vancomycin is the agent for which the greatest cumulative clinical experience is available for the treatment of MRSA bacteremia and endocarditis [8, 9]. Compared to β-lactams, vancomycin has relatively slow bacterial killing, poor tissue penetration, and potential for toxicity, all of which may be responsible for the clinical failures reported [10]. The use of vancomycin plus β-lactam therapy and adjunctive therapy with rifampicin to improve outcomes has proved unsatisfactory, providing little or no overall benefit over standard antibiotic therapy and increasing toxicity [11–13]. In a significant randomized trial [14], daptomycin at a dose of 6 mg/kg once daily was not inferior to standard therapy for the treatment of *S. aureus* bacteremia and endocarditis. Nevertheless, the emergence of resistant strains and subsequent therapeutic failures using a once-daily dose of 6 mg/kg of daptomycin has led to the use of higher doses (8–10 mg/kg once daily) in some centers [7]. Despite the use of high doses, treatment failures due to persistent or relapsing infections have been reported [15]. Therefore, more effective strategies for the treatment of serious staphylococcal infections are urgently needed.

The combination of daptomycin and fosfomycin is an appealing strategy for the treatment of MRSA bacteremia. Fosfomycin has gained attention due to its broad spectrum and bactericidal activity against drug-resistant bacteria, including MRSA [16]. Whereas daptomycin disrupts the cell membrane synthesis of *S. aureus* [17], fosfomycin presents bactericidal activity by inhibiting an early stage of peptidoglycan synthesis [16]. Because daptomycin and fosfomycin have different mechanisms of action, they have a synergistic and rapid bactericidal effect, and no cross-resistance has been observed between the drugs [18]. This synergistic activity may be explained by fosfomycin PBP-1 inhibition [19, 20] and by its ability to modify cell-wall protein composition [21].

In a rabbit model of experimental endocarditis, the combination of daptomycin and fosfomycin proved to be synergistic and rapidly bactericidal against MRSA [22]. Data from small series of patients have shown that the combination of fosfomycin with either β-lactams or daptomycin was superior to standard antibiotic therapy for MRSA bacteremia [23, 24]. However, no randomized trials comparing the efficacy and safety of the combination of daptomycin plus fosfomycin vs daptomycin monotherapy for treatment of MRSA bacteremia have been performed to date.

We designed the current randomized multicenter trial to test the hypothesis that daptomycin plus fosfomycin achieves higher treatment success than daptomycin alone in hospitalized adults with MRSA bacteremia and native valve endocarditis.

METHODS

Study Design and Setting

We performed a randomized (1:1), multicenter, phase 3, superiority, open-label and parallel-group clinical trial of adult inpatients with MRSA bacteremia at 18 Spanish hospitals. Participants were recruited between December 2013 and November 2017. The ethics committee at each participating center approved the study protocol. The trial was conducted in agreement with the Declaration of Helsinki, the guidelines for Good Clinical Practice, and Spanish regulatory requirements. This academic trial is registered with ClinicalTrials.gov NCT01898338, and the protocol has been published elsewhere [25].

Participants

Patients aged ≥18 years with MRSA bacteremia indicated by 1 or more positive blood cultures within the last 72 hours before randomization and with symptoms and signs of infection were eligible for the study. Patients or authorized representatives provided written informed consent. Exclusion criteria included life expectancy ≤24 hours, polymicrobial bacteremia, pneumonia as a source of bacteremia, prosthetic valve endocarditis, severe end-stage liver disease (Child-Pugh class C), New York Heart Association functional classification III/IV, prior history of eosinophilic pneumonia, any clinical condition that required additional antibiotic therapy active against MRSA, or allergy to daptomycin or fosfomycin.

Randomization and Masking

Patients were randomly assigned to receive either 10 mg/kg of daptomycin intravenously daily plus 2 g of fosfomycin intravenously every 6 hours, or to receive 10 mg/kg of daptomycin intravenously daily, between 10 and 14 days for uncomplicated bacteremia and between 28 and 42 days for complicated bacteremia. A centralized electronic computer randomization schedule was developed by the Catalan Institute of Pharmacology. The randomization was performed in computed-generated variable blocks ranging from 4 to 8 patients per center, to conceal the sequence until the intervention was assigned. The code numbers for eligible patients were assigned in ascending sequential order. The allocation list was stored at the Catalan Institute of Pharmacology. At each

participating hospital, patients who provided written informed consent and met the study criteria were randomized by investigators, who obtained the assigned treatment and code number from a computer-assisted website.

Procedures

Daptomycin (Cubicin, Merck Sharp & Dohme B.V., Haarlem, the Netherlands) was administered intravenously by a 30-minute infusion once a day, and fosfomycin (Fosfocina, ERN S.A., Barcelona, Spain), was administered intravenously by at least one 60-minute infusion every 6 hours. Antibiotic dosage was adjusted according to creatinine clearance [25].

Patients were evaluated by researchers at inclusion, day 3, day 7, and end of therapy (EOT), and at the test of cure (TOC) visit 6 weeks after EOT. Blood cultures were obtained at day 3, day 7 (when positive at day 3), EOT, and TOC. Moreover, blood cultures and biochemistry analyses were performed whenever it was considered necessary by the attending physicians and/or researchers, according to the patient's clinical evolution. Echocardiograms were performed at the discretion of the attending physicians. Removal of pacemaker was not specifically recorded, but it was the standard of care when considered the source of bacteremia in all of the participating centers. Definitions of persistent, recurrent, complicated MRSA bacteremia, and endocarditis are provided in the Supplementary Appendix [26, 27].

Outcomes and Measurements

The primary endpoint was treatment success at TOC (6 weeks after EOT). Treatment success was considered when patient was alive and had resolution of clinical manifestations of infection and negative blood cultures at TOC after completion of therapy. Treatment failure was considered in any of the following situations: lack of clinical improvement at day 3 or later after the start of therapy, persistent MRSA bacteremia at day 7 or later, premature discontinuation of therapy due to adverse events (AEs) or based on clinical judgment, recurrent MRSA bacteremia before or at TOC, additional antimicrobial therapy active against MRSA administered before TOC, lack of blood cultures obtained at TOC, and/or death due to any cause before TOC. Only patients without treatment failure could have treatment success. For analysis purposes, patients lost to follow-up (with missing TOC data) were classified as treatment failure.

The secondary endpoints were MRSA bacteremia at day 3, day 7, and/or at TOC; microbiological failure; complicated bacteremia; AEs leading to treatment discontinuation, and mortality due to any cause at day 7 and at TOC. Microbiological failure was considered in the case of persistent bacteremia, recurrent bacteremia, and the emergence of resistance to study drugs during treatment.

Primary and secondary endpoints were assessed by study investigators in the modified intention-to-treat population. A systematic, prioritized, risk-based approach to monitor AEs was developed to ensure that the trial was conducted, recorded, and reported according to good clinical practices [28]. AEs were recorded in all patients who received at least 1 dose of the study medication. Clinical laboratory tests, vital signs, and other safety assessments were performed at scheduled visits. An independent data and safety monitoring committee was established to review data when half of the sample had been recruited. Mortality and serious AEs leading to discontinuation of therapy were considered key safety parameters. After a safety monitoring meeting performed on 25 May 2016, no significant differences in serious events between groups were detected, and a formal recommendation of continuing the study was established by the independent data and safety monitoring committee.

Microbiological methods are detailed in the Supplementary Appendix.

Statistical Analysis

Assuming a level of treatment success of 60% among patients receiving daptomycin alone at TOC, a sample size of 103 patients per group was calculated to reject the null hypothesis of equal effect, with a power of 80% and a significance level of 5%, for a 20% difference in treatment success among patients receiving fosfomycin plus daptomycin. A 20% dropout rate was anticipated. In November 2017, the number of recruited patients was 167 and the dropout rate was <5%. Considering the low dropout rate and the time elapsed since the trial was initiated, the study committee decided to recalculate the sample size. Thus, a size of 81 patients per arm was considered enough to find significant differences of 20% between arms with a power of 80% and an α risk of .05. With this additional information, the trial was closed when 167 patients had been enrolled and followed up. Patients who failed to continue in the study trial because they were randomized in error or received <1 day of antibiotic treatment were considered dropouts. As previously stated, study outcomes were assessed in the modified intention-to-treat population, which included all appropriately randomized patients according to the study inclusion criteria who received ≥24 hours of antibiotic therapy. Main efficacy analyses and the proportion of treatment success at TOC were compared between groups using a 2-sided χ^2 test. Relative risk for study outcomes were calculated and reported with 95% confidence intervals (CIs). The homogeneity of the treatment effect was tested in several subgroups defined in the statistical analysis plan: age, Pitt score, and presence of endocarditis. The incidences of events in secondary, safety, and subgroup analyses were compared using χ^2 test or Fisher exact test. The global benefits and risks of the combination therapy

were evaluated in a post hoc analysis using the approach of the Desirability of Outcome Ranking (DOOR) [29]. The components of this analysis were (1) death before TOC; (2) clinical or microbiological failure; and (3) premature discontinuation of therapy due to AEs or based on clinical judgment. All analyses were performed with a 2-sided significance level of .05 and conducted with the use of R software, version 3.5.

RESULTS

From 16 December 2013 to 27 November 2017, we assessed 674 patients with MRSA bacteremia for eligibility, of whom 507 were not suitable for inclusion (Figure 1). A total of 167 patients were randomly assigned to receive daptomycin plus fosfomycin (82 patients) or daptomycin alone (85 patients). After excluding 12 patients who were randomized in error (5 patients) or did not receive the allocated study drug (7 patients) and consequently were excluded from the primary analysis population, the remaining 155 were included in the modified intention-to-treat population; 74 received daptomycin plus fosfomycin and 81 were given daptomycin alone.

Baseline characteristics of the patients were similar in the 2 treatment groups except for a higher number of patients with chronic kidney disease in the daptomycin alone group (Table 1). Echocardiography was performed in 112 (72%) patients, and a final diagnosis of left-side endocarditis was established in 18 (11.6%) patients in this subgroup. Overall, the median duration of antibiotic therapy since randomization was 14 days (interquartile range [IQR], 10–18 days) (Table 1).

Treatment success at TOC was achieved in 40 of 74 (54.1%) patients who received daptomycin plus fosfomycin and in 34 of 81 (42.0%) patients who were given daptomycin alone (relative risk, 1.29 [95% CI, .93–1.8]; χ^2 test $P = .133$) (Table 2 and Figure 2). Treatment failure at TOC occurred in 34 (45.9%) patients receiving daptomycin plus fosfomycin and in 47 (58%) receiving daptomycin alone ($P = .133$). Reasons for treatment failure at TOC are detailed in Table 3. No cases of clinical or microbiological failure were observed in patients receiving daptomycin plus fosfomycin, whereas 12 patients receiving daptomycin alone had treatment failure (clinical in 3 and microbiological in 9 [0% vs 14.8%]; $P < .001$). More patients receiving daptomycin alone required the administration of nonstudy antibiotics active against MRSA before TOC than those treated with daptomycin plus fosfomycin (23.4% vs 12.1%; $P = .068$).

Subgroup analyses suggested that patients aged <73 years and those with a Pitt score >1 could particularly benefit from receiving the combination of daptomycin plus fosfomycin to achieve treatment success at TOC. No differences were observed in patients with or without endocarditis (Figure 2).

The results for secondary endpoints are shown in Table 2 and Supplementary Figure 3. At day 3 of follow-up, daptomycin plus fosfomycin was significantly associated with lower rates of positive blood cultures than daptomycin alone (2 of 74 patients [2.7%] vs 15 of 81 [18.5%], respectively). At day 7, 0 of 74 patients (0%) who received daptomycin plus fosfomycin vs 5 of 81 patients (6.2%) who received daptomycin alone had persistent bacteremia. Recurrent bacteremia from EOT to the TOC visit occurred in 0 of 74 (0%) patients receiving daptomycin plus fosfomycin vs 4 of 81 (3.7%) who received daptomycin alone. The final microbiological evaluation at TOC found that no patient treated with daptomycin plus fosfomycin had microbiological failure compared with 9 patients treated with daptomycin alone, among whom bacteremia was considered persistent in 5, and recurrent in 4 patients ($P = .003$).

Development of resistance to daptomycin during treatment was documented in 1 patient with persistent bacteremia in the daptomycin alone group; the minimum inhibitory concentration increased from 0.5 mg/L to 2 mg/L. Among the 9 patients with microbiological failure, 6 had consecutive isolates available for pulsed-field gel electrophoresis typing. All pairs of isolates obtained from the same patient showed the same band pattern, and so microbiological failure was considered as a relapse.

Complicated bacteremia at TOC was observed in 12 of 74 patients (16.2%) who had received daptomycin plus fosfomycin and in 26 of 81 (32.1%) who had received daptomycin alone (relative risk, 0.51 [95% CI, .28–.94]; χ^2 test $P = .022$). No significant differences in overall mortality were observed at TOC between patients receiving daptomycin plus fosfomycin and those receiving daptomycin alone (24.3% vs 27.2%; $P = .687$).

Patients receiving daptomycin plus fosfomycin had a higher rate of AEs leading to discontinuation of therapy than patients receiving daptomycin alone (17.6% vs 4.9%; $P = .012$) (Table 4). No differences were observed between the groups at TOC in terms of overall mortality, lack of blood cultures, or loss to follow-up. A total of 103 AEs was recorded in 160 randomized patients who received any dose of study drug (Supplementary Table 5). The number of patients with AEs and serious AEs did not vary between the groups, but there were differences in the frequency of AEs related to the study drugs. The most frequent serious AEs in patients receiving daptomycin plus fosfomycin were cardiac failure in 5 cases and hypokalemia in 2. A 10-fold increase in creatinine phosphokinase values was observed in 1 patient receiving daptomycin plus fosfomycin and in 2 patients receiving daptomycin alone. AEs leading to treatment discontinuation occurred in 13 of 77 patients (16.9%) receiving daptomycin plus fosfomycin and in 4 of 83 patients (4.8%) receiving daptomycin alone ($P = .013$; Table 4). The median time from randomization to discontinuation of the antibiotic treatment due to serious AEs was 10 days (IQR, 4–14 days) in patients receiving daptomycin plus fosfomycin and 10.5 days (IQR, 10–11.5 days) in those given daptomycin alone.

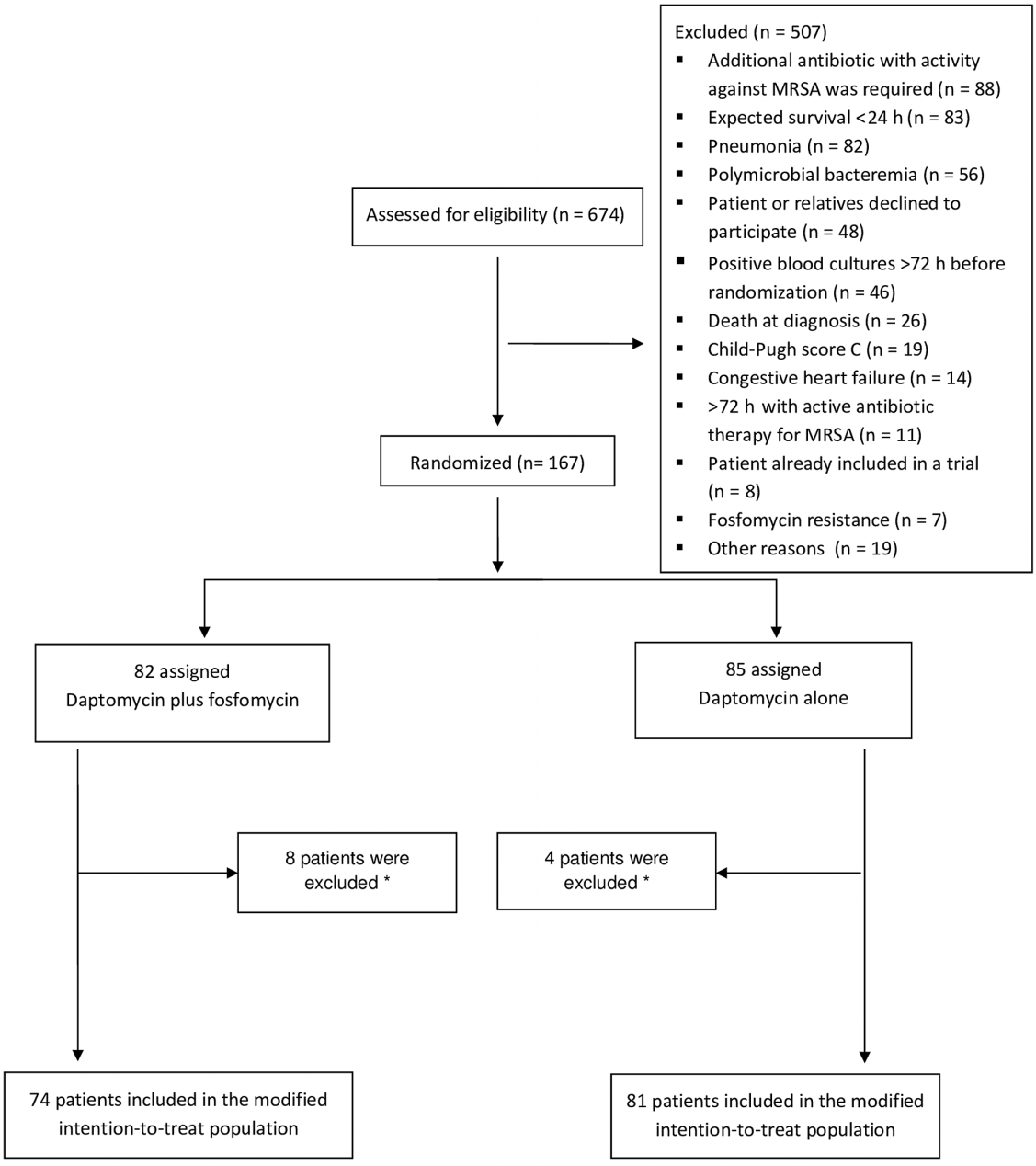

Figure 1. Trial profile. *Reasons for exclusion after randomization were as follows: patient randomized twice (n = 2); positive blood culture >72 hours before randomization (n = 3); patient received <1 day of antibiotic treatment (n = 3); protocol violation (n = 4).

When benefits and risks of the intervention were analyzed by the DOOR approach, the probability that a patient randomly assigned to daptomycin plus fosfomycin combination would have a better DOOR ranking than if assigned to daptomycin alone was 61.6% (95% CI, 60.4%–62.8%).

DISCUSSION

In this randomized clinical trial, daptomycin plus fosfomycin provided a 12% higher rate of treatment success than daptomycin alone at 6 weeks after end of therapy for MRSA bacteremia, but this difference did not reach statistical significance. Of note, the antibiotic combination therapy precluded microbiological failure and complicated bacteremia at TOC but was more often associated with AEs leading to treatment discontinuation. Our results suggest that daptomycin plus fosfomycin could be more effective than daptomycin alone in younger patients and in those with more severe disease, but this needs to be confirmed after further study. Our findings were reinforced by the DOOR post hoc analysis showing that patients randomly assigned to daptomycin plus fosfomycin combination would have a better

Table 1. Characteristics of Patients at Baseline in the Modified Intention-to-Treat Population

Characteristic	Daptomycin Plus Fosfomycin (n = 74)	Daptomycin Alone (n = 81)
Age, y, median (IQR)	74.0 (60.8–80.8)	72 (62.0–80.0)
Male sex	48 (64.9)	56 (69.1)
Charlson comorbidity index, median (IQR)[a]	3 (2–5)	4 (2–5.8)
Diabetes mellitus[b]	29 (30.3)	34 (41.9)
Diabetes mellitus with end organ damage[b]	13 (17.6)	18 (22.2)
Chronic kidney disease[b]	19 (25.7)	35 (43)
Congestive heart failure[b]	13 (17.6)	19 (23.4)
Malignancy[b]	18 (24.3)	16 (19.7)
Pitt score, mean (SD)[c]	1.15 (1.7)	1.22 (2.0)
Implants	20 (27.0)	27 (33.3)
Orthopedic	11 (14.9)	13 (16.0)
Pacemaker	8 (10.8)	4 (4.9)
Previous antibiotic therapy[d]	59 (79.7)	65 (80.2)
Acquisition		
Community-acquired	7 (9.4)	4 (4.9)
Nosocomial infection	36 (48.6)	35 (43.2)
Healthcare-associated	31 (41.8)	42 (51.8)
Main source of infection		
Intravascular catheter	31 (41.9)	39 (48.1)
Skin and soft tissue infection	10 (13.5)	19 (23.5)
Surgical site infection	7 (9.5)	4 (4.9)
Urinary tract infection	6 (8.1)	3 (3.7)
Unknown source	14 (18.9)	8 (9.9)
Other	6 (7.4)	8 (9.9)
Echocardiography	53 (71.6)	59 (72.8)
Endocarditis[e]	9 (12.2)	9 (11.1)
Days of therapy, median (IQR)	14 (11–21)	14 (10–18.5)

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; SD, standard deviation.

[a]Provides a 10-year mortality risk, based on weighted comorbid conditions.

[b]Based on the definitions within the Charlson comorbidity index assessment.

[c]Provides a measure of in-hospital mortality risk in patients with bloodstream infection based on clinical variables.

[d]Based on administration of any antibiotic in the 10 days prior to randomization.

[e]Based on assessment at test-of-cure visit according to modified Duke criteria [27].

Table 2. Primary and Secondary Outcomes

Outcome	Daptomycin Plus Fosfomycin, No. of Patients/Total (%)	Daptomycin Alone, No. of Patients/Total (%)	Relative Risk (95% CI)
Primary endpoint			
Treatment success at TOC	40/74 (54.1)	34/81 (42.0)	1.29 (.93–1.8)
Secondary endpoints			
Positive blood cultures at day 3	2/74 (2.7)	15/81 (18.5)	0.15 (.04–.63)
Positive blood cultures at day 7	0/74 (0.0)	5/81 (6.2)	−6.2 (−11.4 to −.9)[a]
Positive blood cultures at TOC	0/74 (0.0)	4/81 (4.9)	−4.9 (−9.7 to −.2)[a]
Microbiological failure at TOC	0/74 (0.0)	9/81 (11.1)	−11.1 (−18.0 to −4.3)[a]
No. of episodes of complicated bacteremia at TOC	12/74 (16.2)	26/81 (32.1)	0.51 (.28–.94)
Any AE leading to treatment discontinuation	13/74 (17.6)	4/81 (4.9)	3.56 (1.21–10.44)
Overall mortality at day 7	3/74 (4.1)	6/81 (7.4)	0.55 (.14–2.12)
Overall mortality at TOC	18/74 (24.3)	22/81 (27.2)	0.9 (.53–1.54)

Abbreviations: AE, adverse event; CI, confidence interval; TOC, test of cure.

[a]Proportion difference, as it was not possible to estimate the relative risk.

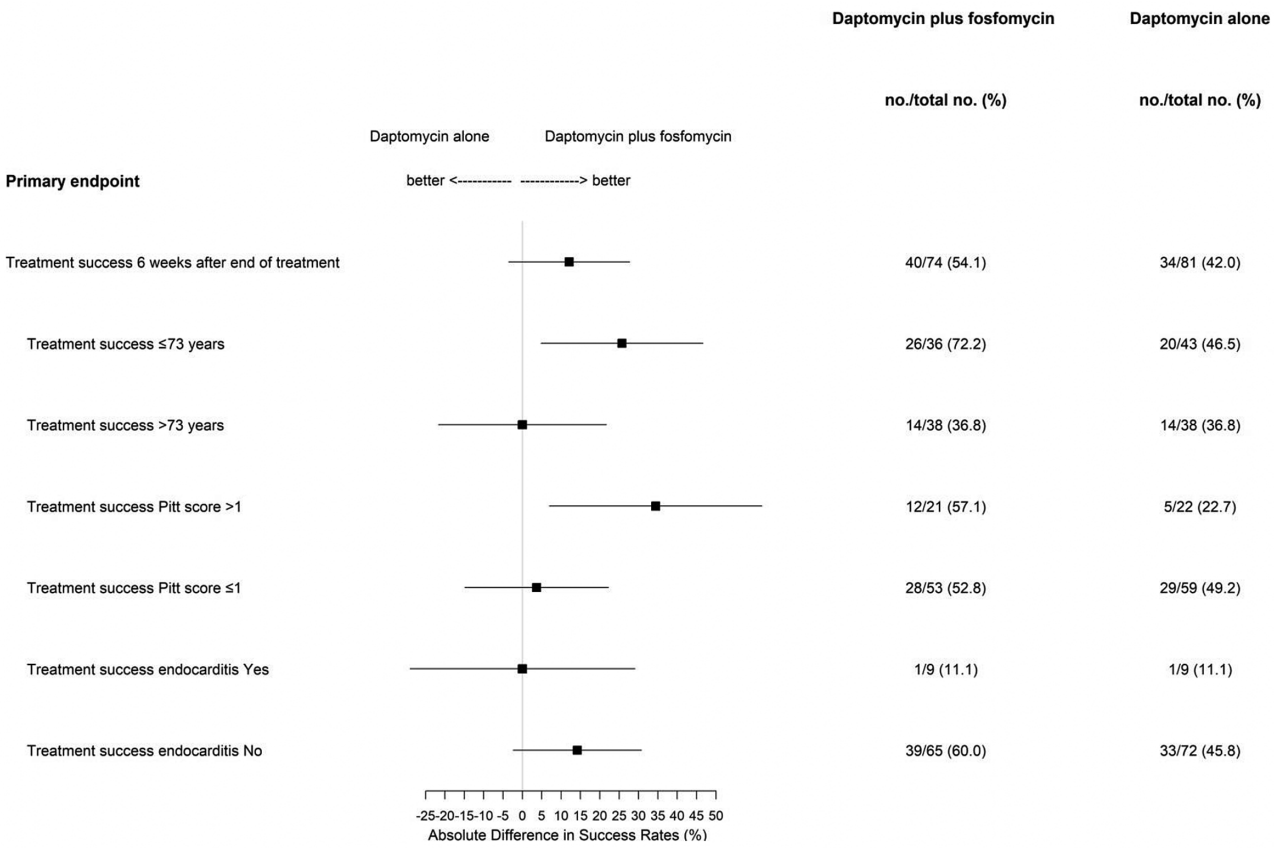

Figure 2. Primary endpoint.

DOOR ranking, and thus a better outcome, than if assigned to daptomycin alone.

We found that no patient receiving daptomycin plus fosfomycin had persistent bacteremia at day 7 and/or relapsing bacteremia at TOC. Rapid clearance of MRSA bacteremia is an important target, since the persistence of positive blood cultures beyond day 3 has been closely related to worse clinical outcomes [30, 31]. Importantly, we found that patients receiving

Table 3. Reasons for Treatment Failure at Test of Cure

Reason for Treatment Failure	Daptomycin Plus Fosfomycin, No. (%) of Patients (n = 74)	Daptomycin Alone, No. (%) of Patients (n = 81)	Proportion Difference (95% CI)	*P* Value[a]
Treatment failure[b]	34 (45.9)	47 (58.0)	−12.1 (−27.7 to 3.6)	.133
Mortality at TOC	18 (24.3)	22 (27.1)	−2.8 (−16.6 to 10.9)	.687
Clinical failure[c]	0 (0.0)	3 (3.7)	−3.7 (−7.8 to .4)	.247[d]
Microbiological failure	0 (0.0)	9 (11.1)	−11.1 (−18.0 to −4.3)	.003[d]
Any AE leading to treatment discontinuation	13 (17.6)	4 (4.9)	12.6 (2.8–22.5)	.012
Additional antimicrobial therapy administered before TOC[e]	9 (12.1)	19 (23.4)	−11.3 (−23.2 to .6)	.068
Lack of blood cultures at TOC	8 (10.8)	4 (4.9)	5.9 (−2.6 to 14.4)	.172
Loss to follow-up	1 (1.3)	3 (3.7)	−2.4 (−7.2 to 2.5)	.622[d]

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: AE, adverse event; CI, confidence interval; TOC, test of cure.

[a]Unless otherwise specified, *P* value derived from χ^2 test.

[b]Patients might have >1 reason for treatment failure (ie, mortality at TOC, clinical or microbiological failure, any AE leading to treatment discontinuation, additional antimicrobial therapy administered before TOC, lack of blood cultures before TOC).

[c]Lack of clinical improvement ≥3 days after the start of therapy.

[d]Fisher exact test.

[e]Receipt of potentially effective nonstudy antibiotics active against methicillin-resistant *Staphylococcus aureus* before TOC visit.

Table 4. Adverse Events Leading to Treatment Discontinuation

Adverse Event	Daptomycin Plus Fosfomycin (n = 77)	Daptomycin Alone (n = 83)	Relation to Antibiotic Treatment
Patients with AE leading to treatment discontinuation, No. (%)	13 (16.9)	4 (4.8)	…
AE leading to treatment discontinuation, No. (%)	16 (20.8)	4 (4.8)	…
Cardiac failure, No.	4	…	R
Hypokalemia (<3 mmol/L), No.	2	…	R
Hypocalcemia (corrected serum total calcium level <2.12 mmol/L), No.	1	…	R
Acute renal failure, No.	1	1	NR
Creatinine phosphokinase increase (>10-fold), No.	1	1	R
Respiratory failure, No.	…	1	NR
Respiratory tract infection, No.	2	1	NR
Acute liver injury, No.	1	…	NR
Severe acute digestive bleeding, No.	1	…	NR
Nausea/vomiting, No.	2	…	R

Abbreviations: AE, adverse event; NR, nonrelated; R, related.

combination therapy developed complicated bacteremia less often and that no antibiotic resistance occurred in any patients in this group. Our results concur with those reported in small series of patients treated with β-lactams or daptomycin plus fosfomycin [23, 24]. Additionally, the combination of daptomycin plus fosfomycin might prevent the emergence of drug resistance. The single patient who developed resistance to daptomycin was receiving daptomycin alone.

We found that AEs leading to treatment discontinuation were more frequent in patients receiving daptomycin plus fosfomycin. The antibiotic combination was more often associated with cardiac failure and electrolyte disorders, particularly hypokalemia and hypocalcemia. It has been suggested that hypokalemia could be avoided in some cases by the extended infusion of fosfomycin over a 4-hour period [32]. The fact that fosfomycin-related serious AEs appeared after a median of 10 days of therapy and the high microbiological efficacy achieved at 3 and 7 days of the combination therapy suggest that fosfomycin should essentially be administered during the first week of treatment.

Our randomized trial has several limitations. The study was not blinded for the investigators, and this might have impact decisions to discontinue the therapy due to clinical worsening or suspected AE. The effect of this potential bias was minimized by including microbiological analyses in the treatment success definition. Furthermore, the study was performed in a single country and this might have limited the generalizability of our results.

In conclusion, daptomycin plus fosfomycin provided a 12% higher rate of treatment success than daptomycin alone, but this difference did not reach statistical significance. Our results suggest that this antibiotic combination could be more effective in younger patients and those with more severe disease. Daptomycin plus fosfomycin precluded microbiological failure and complicated bacteremia but was more often associated with AEs leading to treatment discontinuation.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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