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High-Dose Daptomycin plus Fosfomycin Is Safe and Effective in Treating Methicillin-Susceptible and Methicillin-Resistant *Staphylococcus aureus* Endocarditis

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We describe 3 patients with left-sided staphylococcal endocarditis (1 with methicillin-susceptible *Staphylococcus aureus* [MSSA] prosthetic aortic valve endocarditis and 2 with methicillin-resistant *S. aureus* [MRSA] native-valve endocarditis) who were successfully treated with high-dose intravenous daptomycin (10 mg/kg/day) plus fosfomycin (2 g every 6 h) for 6 weeks. This combination was tested *in vitro* against 7 MSSA, 5 MRSA, and 2 intermediately glycopeptide-resistant *S. aureus* isolates and proved to be synergistic against 11 (79%) strains and bactericidal against 8 (57%) strains. This combination deserves further clinical study.

Daptomycin is approved for the treatment of skin and soft tissue infections, *Staphylococcus aureus* bacteremia, and right-sided native-valve endocarditis (3). There are, however, few data on the efficacy of daptomycin in the treatment of left-sided native-valve endocarditis caused by *S. aureus*. In a randomized clinical trial, only 1 (11%) of 9 patients treated with intravenous (i.v.) daptomycin at 6 mg/kg daily was cured (9). In a registry of patients at 45 U.S. institutions who received daptomycin for any indication, a successful clinical outcome was achieved in 12 (63%) of 19 cases of left-sided endocarditis caused by *S. aureus* (14).

The efficacy of daptomycin in left-sided native- or prosthetic-valve *S. aureus* endocarditis may be improved either by increasing the dose to 10 to 12 mg/kg daily or by achieving synergy by the addition of a second agent. The addition of gentamicin or rifampin did not, however, increase the activity of daptomycin in a rabbit model of methicillin-resistant *S. aureus* (MRSA) endocarditis (18). While fosfomycin is FDA approved only for the treatment of uncomplicated urinary tract infections, it has demonstrated good antimicrobial activity against a broad spectrum of pathogens, including methicillin-susceptible *S. aureus* (MSSA) and MRSA (8). Fosfomycin, which acts by inhibition of an early step in cell wall synthesis, has been used successfully in combination with beta-lactams to treat severe staphylococcal infections (22, 23). It also shows *in vitro* synergy when combined with daptomycin (4).

We describe 3 patients with *S. aureus* endocarditis who were successfully treated with the combination of high-dose daptomycin and fosfomycin, and we present evidence of *in vitro* synergy between these 2 agents.

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The 3 cases are summarized in Table 1. One had MSSA aortic prosthetic-valve endocarditis, and two had MRSA native-valve endocarditis. They were successfully treated with high-dose daptomycin (i.v. at 10 mg/kg/day) plus fosfomycin (i.v. at 2 g every 6 h) for 6 weeks. All 3 patients had multiple extracardiac septic emboli, and two had small perivalvular abscesses. In 2 cases, 7 to 10 days of i.v. high-dose daptomycin failed to produce sterile blood cultures. The third patient (MRSA mitral valve endocarditis) remained bacteremic after 5 days of vancomycin (trough level of 20 μg/ml at day 5); vancomycin was switched to high-dose daptomycin plus fosfomycin because of nephrotoxicity. All isolates were susceptible to daptomycin and fosfomycin. No clinical or biological side effects were observed. None of the patients needed cardiac surgery.

We used seven MSSA strains and seven MRSA strains to perform *in vitro* studies (Table 2). MICs were determined by a microdilution method according to the procedures of the Clinical and Laboratory Standards Institute (2). Time-kill methodology was used to test the activity of daptomycin plus fosfomycin against MSSA and MRSA strains according to previously described criteria (20). Viability counts were performed at 0, 4, 8, and 24 h (12). Synergy, indifference, antagonism, and bactericidal activity were defined as previously described (18).

MIC data are presented in Table 2. Two of the MRSA strains, glycopeptide intermediately resistant *S. aureus* (GISA) PC3 and ATCC 700788, had only intermediate susceptibility to glycopeptides, with a vancomycin MIC of 8 mg/liter. Time-kill data are presented in Table 3 and Fig. 1. The combination of daptomycin and fosfomycin was synergistic against all 7 MSSA strains and was bactericidal against 5 of them at 8 and 24 h (Table 3). Daptomycin and fosfomycin demonstrated synergy against 3 of the 5 MRSA strains and bactericidal activity against 2 of them. Against 1 of the

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TABLE 1 Clinical characteristics and outcomes of 3 patients with *S. aureus* endocarditis treated with a combination of high-dose daptomycin and fosfomycin

Parameter(s)	Patient 1	Patient 2[a]	Patient 3
Age (yr)	54	53	71
Gender	Female	Male	Male
Chronic underlying diseases	Scleroderma, severe pulmonary artery hypertension, elective aortic and mitral double-valve replacement with mechanical prostheses 11 yr ago, MRSE[c] prosthetic-valve endocarditis 10 years ago needing an aortic valve homograft	Diabetes mellitus, HIV-HBV[b] coinfection	Diabetes mellitus, diabetic foot infection, Child-Pugh class B liver cirrhosis, mild mitral regurgitation due to severe valve calcification
Drug allergies	Penicillin, vancomycin	None	None
Source of infection	Unknown	Left inguinal infection by MRSA 2 weeks after lymph node biopsy	MRSA-infected foot ulcer
Clinical characteristics	High-grade fever, cerebral and splenic emboli, coma, additive EuroSCORE[e] of 18	High-grade fever, malaise, pain in neck and index finger of left hand	High-grade fever, splenic emboli
Blood cultures before treatment	6/6 positive for MSSA	6/6 positive for MRSA	6/6 positive for MRSA
Antibiotic susceptibilities (MIC, μg/ml)	Vancomycin, 1; fosfomycin, 8; daptomycin, 1	Vancomycin, 1.5; fosfomycin, ≤ 32; daptomycin, 1	Vancomycin, 1.5; fosfomycin, ≤ 32; daptomycin, 1
TEE[d] findings	1-cm aortic homograft valve vegetation, 10 by 8 mm perivalvular abscess, no prosthetic valve dysfunction	Calcification of aortic and mitral valves, no evidence of vegetations or perivalvular abscesses	Mitral valve rupture with severe regurgitation, 1-cm mitral valve vegetation, 6 by 8 mm perivalvular abscess
Initial i.v. antibiotic therapy (no. of days)	Daptomycin at 10 mg/kg/day (7)	Daptomycin at 4 mg/kg/day (2), daptomycin at 4 mg/kg/day plus gentamicin at 240 mg/48 h (5), daptomycin at 8 mg/kg/day plus gentamicin at 240 mg/48 h (3)	Vancomycin at 15 mg/kg every 12 h; vancomycin trough plasma concentrations, 11 and 20 μg/ml on days 2 and 5, respectively
Complications of first-line treatment	None	Progressive renal failure; need for hemodialysis; signs of septic embolization along left sternal margin and on first left metacarpal joint, second and third right toes, right forefoot, and left sternocleidomastoid muscle at day 2; pyomyositis with compression of oropharynx at day 10	Serum creatinine increase from 1.4 to 3.0 mg/dl (normal, ≤1.3 mg/dl) during first 24 h but return to normal level after 2 days
Follow-up blood cultures after initial treatment	Positive at days 3, 7	Positive at days 3, 7, 10	Positive at day 5
No. of days from initial treatment to switch to daptomycin plus fosfomycin	7	10	5
Doses given i.v. (daptomycin, fosfomycin)	10 mg/kg/day, 2 g/6 h	10 mg/kg/day, 2 g/6 h	10 mg/kg/day, 2 g/6 h
Time of first negative blood cultures after switch to daptomycin plus fosfomycin (h)	72	48	48
Duration of treatment (wk)	8	6	6
Complications of daptomycin plus fosfomycin treatment	None	Transmetatarsal amputation of right foot, chronic hemodialysis	None
Follow-up blood cultures after daptomycin plus fosfomycin	Negative at days 14, 42	Negative at days 14, 28, 42, 90	Negative at days 30, 90
Clinical follow-up	Alive at 1 yr	Alive at 1 yr	Alive at 6 mo

[a] Patient 2 could be considered to have possible endocarditis according to the Duke criteria.
[b] HBV, hepatitis B virus.
[c] MRSE, methicillin-resistant *S. epidermidis*.
[d] TEE, transesophageal echocardiography.
[e] See references 7 and 16.

TABLE 2 *S. aureus* strains tested and MICs

Strain[a]	MIC (μg/ml)		
	Daptomycin	Fosfomycin	Vancomycin
MSSA 1112	0.5	8	1
MSSA P3	0.5	4	1
MSSA P4	0.5	8	1
MSSA P7	0.5	8	1
MSSA 4297	0.5	1	1
MSSA RN4220	0.5	4	0.5
MSSA 678	1	8	1
MRSA 277	0.25	4	2
MRSA P8	0.5	4	1
MRSA 2167	0.5	16	2
MRSA 4194	0.25	8	1
MRSA 726	0.25	16	0.5
GISA PC3	2	8	8
GISA ATCC 700788	0.5	16	8

[a] All isolates were stored at −80°C in skim milk prior to testing. Daptomycin susceptibility testing was performed in Mueller-Hinton broth (MHB) adjusted to 50 μg/ml calcium in accordance with the standard methodology. Fosfomycin susceptibility testing was performed in MHB supplemented with 25 μg/ml glucose-6-phosphate in accordance with the standard methodology. *S. aureus* ATCC 29213 was used as the control strain. MSSA RN4220, GISA PC3, and GISA ATCC 700788 were used as reference strains. The remaining 11 strains were isolated from the blood of patients with *S. aureus* endocarditis (1 isolate per patient). MSSA 678 was from case 1, and MRSA 726 was from case 3 (see Table 1).

2 GISA strains, ATCC 700788, daptomycin and fosfomycin demonstrated both synergy and bactericidal activity at 24 h; against strain PC3, the combination was both synergistic and bactericidal at 4 and 8 h but only synergistic at 24 h (Table 3).

Infective endocarditis caused by *S. aureus* causes considerable

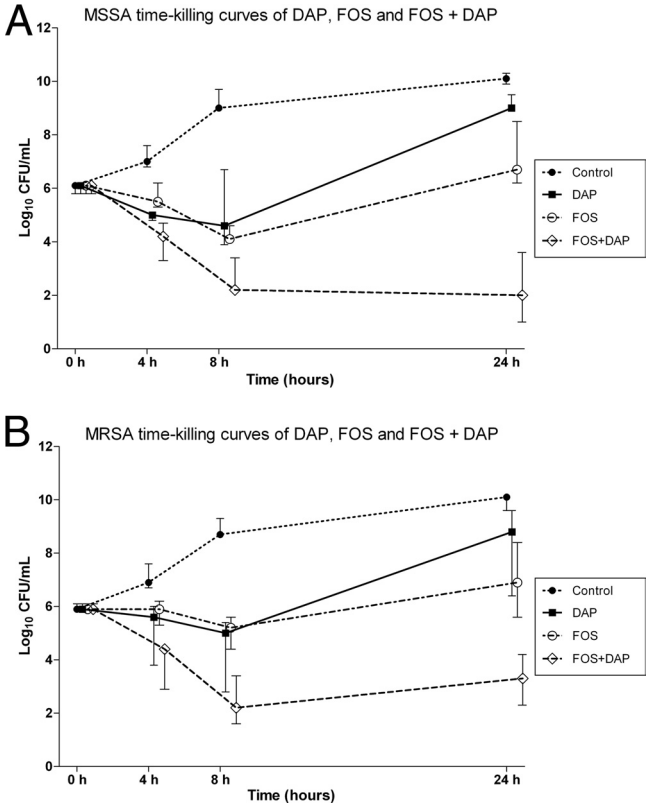

FIG 1 Time-kill curves of fosfomycin (FOS), daptomycin (DAP), and FOS plus DAP for 7 MSSA (A) and 7 MRSA (B) strains. Each result is expressed as a median and the interquartile range. Antibiotic concentrations were tested at the MIC, except for 2 MSSA strains (1112 and P7), where DAP was tested at 0.5 times the MIC.

TABLE 3 MSSA and MRSA time-kill curves at antibiotic MICs[a]

Strain (baseline [0 h] $\log_{10}$ no. of CFU/ml)	Change in $\log_{10}$ CFU/ml											
	Control			Fosfomycin			Daptomycin			Fosfomycin + daptomycin		
	4 h	8 h	24 h	4 h	8 h	24 h	4 h	8 h	24 h	4 h	8 h	24 h
MSSA strains												
MSSA 1112 (6.1)	+0.9	+3.6	+4.1	+0.1	−2.1	+0.4	−1.2	−1.1	+2.9	−1.7	−3.9	−2.5
MSSA P4 (5.8)	+2	+4.1	+4.6	−0.3	−1.7	+1.2	−0.8	−1.1	+3.7	−4.2	−4.8	−4.8
MSSA P5 (6)	+0.8	+3.6	+4.3	−0.5	−2	+3.5	−2.2	−2.4	+3.4	−2.7	−3.9	−5
MSSA P7 (6.1)	+0.9	+2.9	+4	−0.8	−2.5	+0.1	−0.8	+0.6	+2.9	−1.9	−3.7	−3.3
MSSA 4297 (6.3)	+0.7	+2.7	+3.8	−0.2	−1.3	+2.2	−1.3	−2.4	+2.7	−1.6	−2.9	−1.7
MSSA RN4220 (5.7)	+0.8	+3.1	+4.2	−5.4	−1.1	−0.7	−1.2	−2.4	+3.8	−1.8	−3.6	−4.7
Patient 1 MSSA 678 (6.1)	+1.5	+2.9	+3	+0.1	−1.5	+0.6	−1	−2	+2.6	−1.1	−2.1	−4.1
MRSA strains												
MRSA 277 (5.6)	+1.1	+3	+4.5	+0.2	−0.3	+3	−0.8	−1.1	+4	−1.2	−3.4	−2.3
MRSA P8 (6.1)	+1.5	+3.4	+4.1	−0.8	−1.8	−1.2	−2.3	−3.3	−1.1	−3.4	−4.5	−3.2
MRSA 2167 (6)	+1	+3.3	+4.3	−0.7	−1.5	+0.2	−2.2	−3.2	+0.4	−3	−3.6	−1.8
MRSA 4194 (5.9)	+1	+3.4	+4.2	+0.5	+0.7	+1	+0.1	−0.9	+3.1	0	−1.4	−1.8
Patient 3 MRSA 726 (6.1)	+1.5	+2.6	+2.9	−0.2	−1.7	−0.5	+0.6	+1.9	+2.7	−1.6	−2.7	−4.1
GISA PC3 (5.9)	+0.5	+2.1	+4.1	+0.2	−0.3	+1.9	−0.1	−0.9	+2.5	−3	−4.6	−1.5
GISA ATCC (5.9)	+1	+2.7	+4	+0.3	−0.7	+2.5	−0.3	−0.5	+3.8	−1.4	−4	−3.6

[a] Antibiotics were used alone and in combination at the MIC of each drug for the organism. If the MIC of a single drug eliminated viable organisms at 24 h, a concentration of 0.5 times the MIC was used so that the effect of a single drug would not obscure that of a drug combination. Daptomycin was tested at 0.5 times the MIC for two MSSA strains (1112 and P7) and one MRSA strain (726). Synergy was defined as a ≥2-$\log_{10}$ decrease in the number of CFU/ml between the combination and the most active agent tested alone and as a ≥2-$\log_{10}$ decrease in the colony count from the starting inoculum after 8 or 24 h. Indifference was defined as a <2-$\log_{10}$ change (increase or decrease) in the number of CFU/ml after 24 h between the combination and the most active agent tested alone. Antagonism was defined as a ≥2-$\log_{10}$ increase in the number of CFU/ml after 8 or 24 h between the combination and the most active agent tested alone. Bactericidal activity was defined as a decrease of ≥3 $\log_{10}$ CFU/ml after 24 h of incubation. The lower limit of detection for time-kill assays was 1 $\log_{10}$ CFU/ml.

morbidity and mortality (10, 17). Treatment options, particularly for cases caused by MRSA, remain limited. The recently issued Infectious Diseases Society of America guidelines (15) recommend 6 weeks of either vancomycin or daptomycin at 6 mg/kg daily for the treatment of native-valve endocarditis caused by MRSA; the use of higher doses of daptomycin (8 to 10 mg/kg daily) were also considered. Along with increased doses, the addition of a second agent may provide synergy and thus enhance efficacy. Fosfomycin, a phosphonic acid derivative first identified in 1969 (11), has good tissue penetration and low protein binding and is available in an i.v. formulation (23). While it has demonstrated *in vitro* synergy in combination with a number of antibacterial agents, including daptomycin, against a variety of Gram-positive and -negative organisms (21–23), data on the use of the combination in patients are limited.

The initial failure of high-dose daptomycin (cases 1 and 2) and of vancomycin (case 3) may be explained by the high inoculum associated with disseminated staphylococcal infections and the difficulty of achieving adequate drug levels in sequestered foci of infection such as valve vegetations and abscesses. Therefore, these patients may have been ideal candidates for the synergistic action of two agents. Similar clinical conditions were identified by Fowler et al. (9) in those patients who had microbiological failure on daptomycin. While we did not see an increase in daptomycin MICs in our cases, the combination of daptomycin and fosfomycin has also proven effective, both *in vitro* and clinically, against daptomycin-nonsusceptible isolates of *S. aureus* (1, 13). These two agents interfere with different steps; fosfomycin inhibits peptidoglycan (cell wall) synthesis, while daptomycin acts via membrane depolarization (5, 19). Although the exact mechanism of synergy is unknown, it could involve a decrease in the positive surface charge of *S. aureus*, which in turn favors daptomycin membrane binding. This mechanism of action was demonstrated *in vitro* by Dhand et al. (6) in a daptomycin-nonsusceptible MRSA strain (MIC, 2 to 4 mg/liter) using the combination of daptomycin plus nafcillin, which is also an anti-staphylococcal cell wall agent.

In conclusion, the 3 cases discussed here and the *in vitro* results provide encouraging evidence that the combination of high doses of daptomycin plus fosfomycin can be effective in the treatment of both native- and prosthetic-valve endocarditis caused by MSSA or MRSA. This combination deserves further clinical study.

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