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Fosfomycin-Daptomycin and Other Fosfomycin Combinations as Alternative Therapies in Experimental Foreign-Body Infection by Methicillin-Resistant *Staphylococcus aureus*

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The efficacy of daptomycin, imipenem, or rifampin with fosfomycin was evaluated and compared with that of daptomycin-rifampin in a tissue cage model infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Strain HUSA 304 was used. The study yielded the following results for MICs (in μg/ml): fosfomycin, 4; daptomycin, 1; imipenem, 0.25; and rifampin, 0.03. The study yielded the following results for minimum bactericidal concentration (MBC) (in μg/ml): fosfomycin, 8; daptomycin, 4; imipenem, 32; and rifampin, 0.5. Daptomycin-rifampin was confirmed as the most effective therapy against MRSA foreign-body infections. Fosfomycin combinations with high doses of daptomycin and rifampin were efficacious alternative therapies in this setting. Fosfomycin-imipenem was relatively ineffective and did not protect against resistance.

The results of animal tissue cage infection models (1, 2) support the use of the combination daptomycin-rifampin as the reference treatment in patients with difficult-to treat foreign-body infections (FBI) caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

However, if daptomycin or rifampin cannot be administered in clinical practice, recent experimental and clinical results propose fosfomycin as a potential alternative, always in combined therapies, to prevent resistance (3–6). Among these combined therapies, the fosfomycin–beta-lactam combination showed enhanced efficacy (7–10), even though the use of beta-lactams against MRSA is discouraged.

We tested the efficacy of fosfomycin combined with standard and high doses of daptomycin (equivalent to 6 and 10 mg/kg of body weight/day in humans, respectively), imipenem, or rifampin in comparison with the reference treatment (daptomycin-rifampin) in a tissue cage model of MRSA infection.

MRSA strain HUSA 304 (ATCC BAA-39) was used for all *in vitro* and *in vivo* studies. MICs and minimal bactericidal concentrations (MBCs) for bacteria in the log phase (inoculum of 10^5 CFU/ml) were determined using standard recommendations (11), and MBCs for bacteria in the log phase at a higher inoculum (10^8 CFU/ml) and in the stationary phase were determined using methodology described elsewhere (12, 13). The results are presented in Fig. 1.

Kill curves were also determined in the log phase (inocula of 10^5 CFU/ml and 10^8 CFU/ml) and in the stationary phase using methodology described elsewhere (12, 14). Fosfomycin and rifampin alone showed similar behavior and were bactericidal only with the standard inoculum adjusted to 10^5 CFU/ml. Their efficacy was altered by inoculum size, stationary phase, and emergence of resistance; however, both showed a notable final killing of 2 log CFU/ml in the stationary phase. Imipenem had bactericidal activity only with low inocula but with an MBC as high as 32 μg/ml. Corroborating previous reports (15), daptomycin was the only drug with bactericidal activity in the log and stationary phases. The results of some combinations are shown in Fig. 1. To our knowledge, the activity of these combinations in the stationary phase has not been reported to date; we found that all combinations exerted an indifferent effect.

The animal model was approved by the Ethical Committee for Animal Experiments at the University of Barcelona. A 72-hour tissue cage rat infection model previously standardized and reported by our group (1) was used. Briefly, two Teflon tissue cages with two polymethylmethacrylate coverslips (CV) each were subcutaneously implanted in Wistar rats. After 3 weeks, the tissue cage fluid (TCF) was percutaneously infected with 0.1 ml of a MRSA preparation (10^6 CFU/ml). At 72 h postinoculation (designated day 1), TCF was obtained to quantify bacterial counts; therapy was then started and administered intraperitoneally for 7 days. At 1 and 4 days after the end of treatment (days 8 and 11, respectively) TCF was again recovered to quantify bacterial counts. On day 11, animals were sacrificed; CV were then removed and processed, as described previously (1), to quantify adherent bacteria and the infection cure rate.

A total of 130 animals were used in 260 tissue cages and divided into therapeutic groups (pharmacokinetic/pharmacodynamic [PK/PD] parameters are in Table 1). As some tissue cages were lost due to spontaneous shedding, 240 cages remained at the start of experiments (day 1) with no significant differences between groups (Table 1). All treatment groups performed better than controls and imipenem ($P < 0.05$). The decreases in TCF bacterial counts at days 8 and 11 are shown in Fig. 2. Results of testing the efficacy against adherent bacteria from CV are presented in Fig. 3, and those of the appearance of resistant isolates are presented in Table 2.

The *in vivo* results confirmed the greater efficacy of the dapto-

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TABLE 1 Pharmacokinetic-pharmacodynamic (PK/PD) parameters of therapeutic groups and bacterial counts from TCF at the beginning of treatment (day 1)[a]

Therapeutic group (*n*)	Bacterial count[b]	Serum		TCF				Equivalent value for humans
		C_{max} (mg/liter)	AUC_{0-24h} (mg/h/liter)	C_{max} (mg/liter)	Trough (mg/liter)	AUC_{0-24h} (mg/h/liter)	T>MIC (%)	
FOS, 500 mg/kg/12 h ($n = 18$)	6.60 ± 1.04	263	620	112	8.8	808	ND	8 g/day
D100, 100 mg/kg/day ($n = 26$)	6.40 ± 0.94	140	1200	40	18	1100	ND	10 mg/kg/day
D45, 45 mg/kg/day ($n = 26$)	6.35 ± 0.92	103	795	26	10	830	ND	6 mg/kg/day
RIF, 25 mg/kg/12 h ($n = 23$)	6.19 ± 0.86	24	277	6.6	3.8	304	ND	900 mg/day
IMI, 120 mg/kg/12 h ($n = 15$)	7.08 ± 0.80	81	ND	32	1.1	ND	100	2 g/day
FOS+D100 ($n = 20$)	6.50 ± 0.92							
FOS+D45 ($n = 20$)	6.45 ± 0.74							
FOS+RIF ($n = 19$)	6.78 ± 0.90							
FOS+IMI ($n = 30$)	7.00 ± 0.98							
D100+RIF ($n = 25$)	6.13 ± 0.66							
CON ($n = 20$)	6.66 ± 1.04							

[a] Abbreviations: C_{max}, peak concentration; AUC_{0-24h}, the area under the concentration-time curve over 24 h; T>MIC, the time the drug concentration remained above the MIC; ND, not determined. Abbreviations for therapeutic groups are defined in the Fig. 2 legend. All of the methodology used for PK/PD studies has been described elsewhere (16). On the basis of previous reports (17, 18), we used the dose of antibiotic that achieved PD parameters in the TCF close to those in human serum; we adjusted the AUC/MIC ratios for all drugs except IMI, for which we selected a dose previously used in rats that mimics the usual dosage in humans due to difficulties in optimizing the PD parameters against the MRSA strain (19).

[b] Mean log CFU/ml ± standard deviation from TCF at day 1.

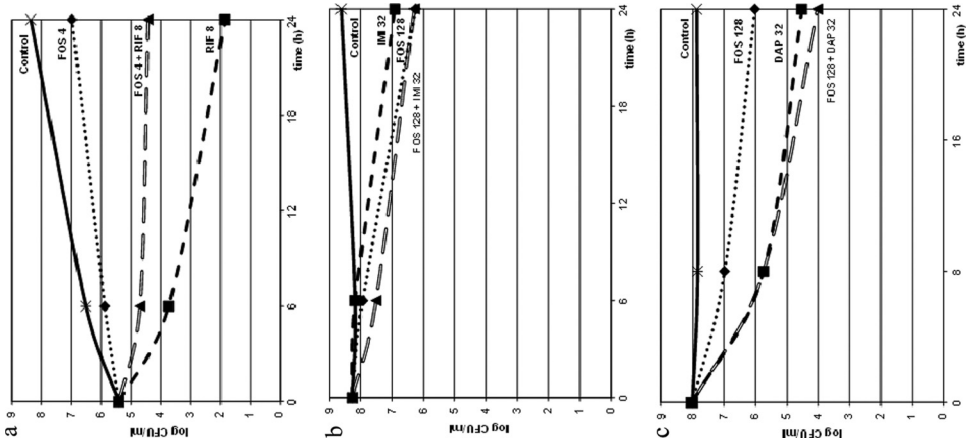

FIG 1 MICs, MBCs, and time-kill curves with the antibiotics alone and in combination with fosfomycin (FOS). Powdered antibiotics were resuspended in sterile water in all cases but rifampin (in methanol). In experiments with FOS and daptomycin (DAP), Mueller-Hinton broth was supplemented with 25 mg/liter of glucose-6-phosphate and with 50 mg/liter of calcium, respectively. MICs (μg/ml) were 1 for DAP, 4 for FOS, 0.25 for imipenem (IMI), and 0.03 for rifampin (RIF). MBCs (μg/ml) in log phase with an inoculum of 10^5 CFU per ml, in log phase with 10^8 CFU per ml, and in stationary phase were, respectively, 4, 20, and 24 for DAP; 8, >128, and >128 for FOS; 32, >128, and >128 for IMI; and 0.5, >8, and >8 for RIF. For the time-kill curves, fixed concentrations of antibiotics (in μg/ml) were used: (i) for log phase, all concentrations included in the range from 0.25× to 512× the MIC, and (ii) for stationary phase, concentrations equivalent to the peak and trough total levels achieved in the TCF (Table 1). Bactericidal activity was equal to a ≥3 log 10 decrease in the initial inoculum in CFU/ml at 24 h. Synergy, indifference, and antagonism were equal to a ≥2 log increase, a <2 log change (increase or decrease), and a ≥2 log decrease, respectively, in killing of the combination in comparison with that of the most active single drug. To avoid carry-over antimicrobial agent interference, the sample was placed on the plate in a single streak down the center and allowed to absorb into the agar until the plate surface appeared dry; then it was spread over the plate. This method has been checked by comparing the results with bacterial counts obtained after the centrifugation of sample and resuspension with physiological serum from pelleting (28). (a) Log phase (inoculum of 10^5 CFU/ml). FOS antagonized the bactericidal effect of RIF. (b) Log phase (inoculum of 10^8 CFU/ml). FOS plus IMI had a synergistic and bactericidal effect against standard inocula but was indifferent and did not protect the emergence of FOS resistance when using high inocula. (c) Stationary phase. DAP plus FOS showed a bactericidal activity, but the effect was indifferent regarding DAP in isolation.

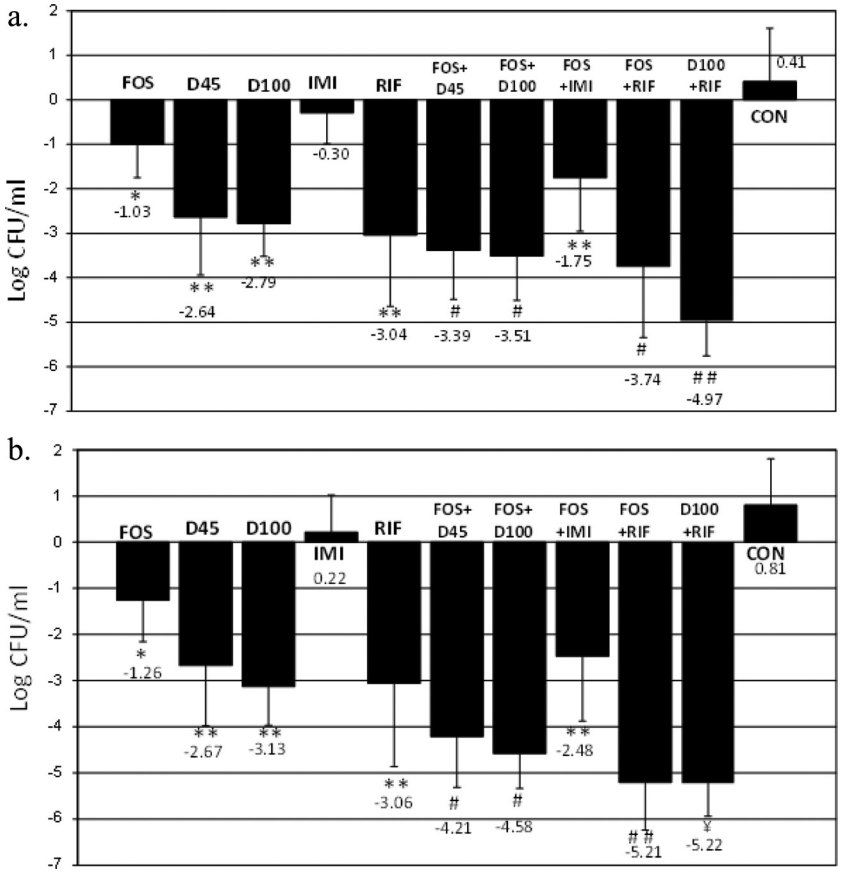

FIG 2 Decreases in bacterial counts from TCF samples (mean of log CFU/ml) at the end of therapy (days 8 and 11). Analysis of variance and an unpaired Student *t* test with Bonferroni correction were used to determine statistical significance (defined as a *P* value of <0.05). Lower limit of detection of bacterial counts, 10 CFU/ml. Abbreviations: FOS, fosfomycin 500 mg/kg/12 h; D45, daptomycin 45 mg/kg/day; D100, daptomycin 100 mg/kg/day; IMI, imipenem 120 mg/kg/12 h; RIF, rifampin 25 mg/kg/12 h; CON, control group. (a) Day 8. The combination of D100 and RIF (D100+RIF) was the most effective treatment (##, $P < 0.05$ versus all therapies). D45, D100, and RIF in combination with FOS were better than either monotherapy or FOS+IMI (#, $P < 0.05$). Results for all drugs were significantly improved by their use in combination (versus their use as monotherapies): D45, D100, and RIF were the most effective (**, $P < 0.05$ versus IMI and FOS), FOS had modest efficacy (*, $P < 0.05$ versus IMI), and IMI was ineffective. (b) Day 11. The efficacy of all groups except IMI, RIF, and D45 was greater than on day 8. D100+RIF had greater efficacy than all therapies but FOS+RIF (¥, $P < 0.05$). FOS+RIF was more effective than all monotherapies, FOS+IMI and FOS+D45 (# #, $P < 0.05$), and FOS+D100 (# #, $P = 0.06$). FOS plus daptomycin (both dosages) was better than all monotherapies and FOS+IMI (#, $P < 0.05$). D45, D100, RIF, and FOS+IMI were more effective than IMI and FOS (**, $P < 0.05$). *, $P < 0.05$ for FOS versus IMI.

mycin-rifampin combination compared with alternative anti-MRSA therapies.

When this combination cannot be applied in clinical practice, fosfomycin is a promising alternative (3–6). Its use is controversial due to concerns regarding its dosage, its PK/PD characteristics, its clinical efficacy against FBI, and the risk of emergence of resistance when administered in isolation (5, 20, 21). We reproduced the pharmacokinetic parameters of a dose of 8 g/day, the amount used in another study of the combination daptomycin-fosfomycin, which had proved synergistic and efficacious in patients with bacteremia and endocarditis caused by MRSA (6). Fosfomycin proved highly effective in an experimental model of osteomyelitis caused by MRSA, in which no resistance was recorded and the addition of daptomycin did not improve final efficacy (22, 23). To our knowledge, no previous data have been reported in the setting of staphylococcal FBI. In our model, fosfomycin alone showed very modest activity with a high proportion of resistant isolates. In contrast, the combination daptomycin-fosfomycin was among the most active, with only daptomycin-rifampin being significantly more effective. The results of the efficacy evaluation against bacteria from TCF at day 11 and the cure rate underline the benefits of high doses of daptomycin in combination.

Although the use of beta-lactams against MRSA is discouraged, previous works reported good efficacy when they were used in association with daptomycin and fosfomycin against bacteremia, endocarditis, and peritonitis (7–10, 24). In contrast, the efficacy of this antibiotic in combination against FBI is little known (12, 21). Herein, we showed that fosfomycin-imipenem was relatively ineffective and did not prevent resistance. These results highlight the differences in the activity of antibiotics against infections involving high inocula of planktonic bacteria (e.g., endocarditis) and those with lower inoculums of nongrowing bacteria (e.g., FBI) (2, 12).

Our *in vitro* results and those of others (25, 26) did not clearly reproduce the *in vivo* efficacy of the fosfomycin-rifampin combination, probably because the antagonism effect against planktonic bacteria did not correlate with the efficacy observed in the FBI model. However, the combination exhibited a killing of 2 log

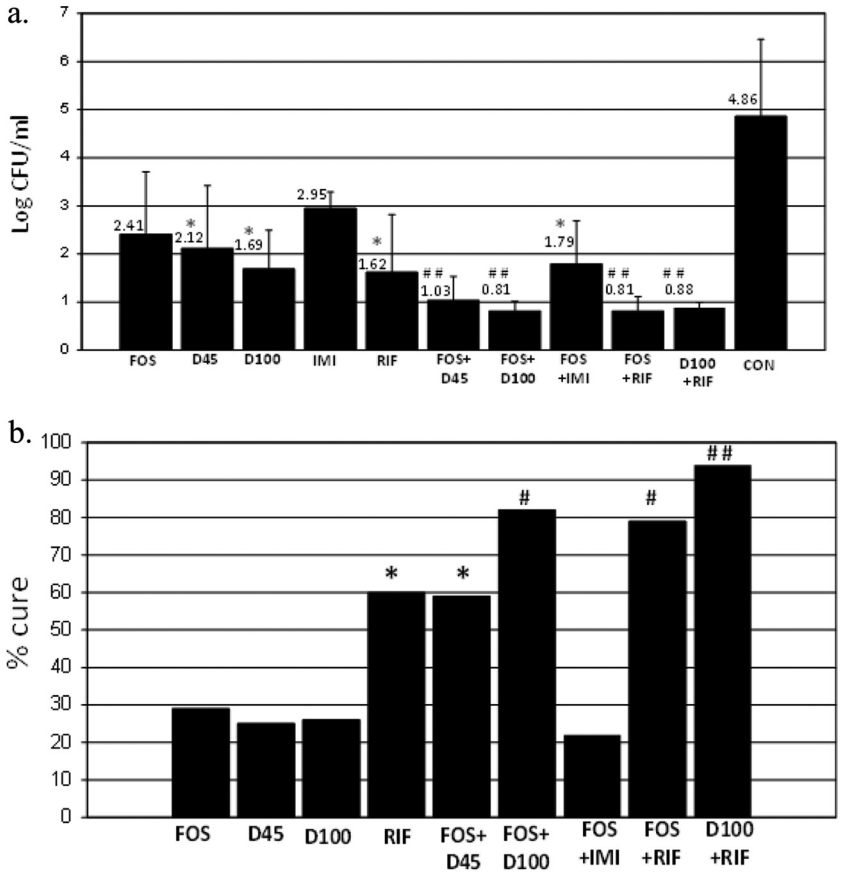

FIG 3 (a and b) Bacterial counts in CV (mean log CFU/ml) (a) and cure rates of infection (expressed as percentages of samples with bacterial counts under the limit of detection with respect to the total samples) (b) for different groups. (a) Results for all groups were better than results for controls ($P < 0.05$). D45, D100, RIF, and FOS+IMI were better than IMI alone (*, $P < 0.05$). All FOS combinations (except FOS+IMI) and D100+RIF were the best therapies (# #, $P < 0.05$ versus all therapies). (b) Results for all groups except IMI (cure rate, 0%; not represented) were better than results for controls ($P < 0.05$). D100+RIF (# #, $P < 0.05$ versus all monotherapies, FOS+IMI, and FOS+D45) was the most effective treatment (94%), and it had greater efficacy than FOS+RIF (79%) and FOS+D100 (82%) (#, $P < 0.05$ versus D45, D100, FOS, and FOS+IMI). Among monotherapies, RIF was the most active therapy (*, $P < 0.05$ versus D45, D100, and FOS+IMI). Abbreviations are defined in Fig. 2.

CFU/ml in the stationary phase and protected against resistance. In fact, only daptomycin-rifampin was significantly more effective than this combination, and fosfomycin-rifampin was not significantly more effective than fosfomycin-daptomycin when the latter was used at high doses. Similarly positive preliminary results were recently reported using a guinea pig model of tissue cage MRSA infection (27).

In conclusion, despite the fact that a limitation of our study is the use of only one MRSA strain, our results confirmed daptomycin-rifampin as the most effective therapy against FBI caused by MRSA. The daptomycin-fosfomycin combination in high doses significantly improved the efficacy of each antibiotic alone and is a good alternative treatment when rifampin cannot be used. Fosfomycin-rifampin also proved as effective as daptomycin-fosfomycin, and both should be considered anti-MRSA therapies in this setting. In contrast, fosfomycin-imipenem was relatively ineffective and did not protect against resistance.

TABLE 2 Resistance studies from TCF and CV at the end of therapy (day 11)[a]

Treatment group[b]	TCF (%)	CV (%)	MIC (μg/ml)
DAP 45	9	4	2
RIF	25	10	≥8
FOS	55	7	≥16
IMI	92	90	≥32
FOS+IMI	50 (FOS), 67 (IMI)	10 (FOS), 15 (IMI)	≥16 (FOS), ≥32 (IMI)

[a] The screening of resistant strains was performed using methodology previously described (1) with agar plates containing 4 μg/ml for FOS and 1 μg/ml for DAP, IMI, and RIF. The plates for experiments with FOS and DAP were supplemented with 25 mg/liter of glucose-6-phosphate and 50 mg/liter of calcium, respectively. Results were interpreted as positive (some macroscopic growth) or negative (no growth) and presented as percentages of positive samples versus total samples. Only therapeutic groups with appearance of resistant strains are presented in this table.
[b] Abbreviations for therapeutic groups are defined in the Fig. 2 legend.

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