Efficacy and Safety of Fosfomycin Plus Imipenem as Rescue Therapy for Complicated Bacteremia and Endocarditis Due to Methicillin-Resistant Staphylococcus aureus: A Multicenter Clinical Trial

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Background. There is an urgent need for alternative rescue therapies in invasive infections caused by methicillin-resistant Staphylococcus aureus (MRSA). We assessed the clinical efficacy and safety of the combination of fosfomycin and imipenem as rescue therapy for MRSA infective endocarditis and complicated bacteremia.

Methods. The trial was conducted between 2001 and 2010 in 3 Spanish hospitals. Adult patients with complicated MRSA bacteremia or endocarditis requiring rescue therapy were eligible for the study. Treatment with fosfomycin (2 g/6 hours IV) plus imipenem (1 g/6 hours IV) was started and monitored. The primary efficacy endpoints were percentage of sterile blood cultures at 72 hours and clinical success rate assessed at the test-of-cure visit (45 days after the end of therapy).

Results. The combination was administered in 12 patients with endocarditis, 2 with vascular graft infection, and 2 with complicated bacteremia. Therapy had previously failed with vancomycin in 9 patients, daptomycin in 2, and sequential antibiotics in 5. Blood cultures were negative 72 hours after the first dose of the combination in all cases. The success rate was 69%, and only 1 of 5 deaths was related to the MRSA infection. Although the combination was safe in most patients (94%), a patient with liver cirrhosis died of multiorgan failure secondary to sodium overload. There were no episodes of breakthrough bacteremia or relapse.

Conclusions. Fosfomycin plus imipenem was an effective and safe combination when used as rescue therapy for complicated MRSA bloodstream infections and deserves further clinical evaluation as initial therapy in these infections.

Keywords. MRSA; bacteremia; infective endocarditis; fosfomycin; imipenem.

Staphylococcus aureus is the leading cause of bacteremia and infective endocarditis (IE). About 20%–50% of clinical S. aureus isolates in the United States and most European countries are resistant to methicillin [1, 2]. Methicillin-resistant S. aureus (MRSA) bloodstream infections are associated with mortality rates of 30%–50% [3], thus making them a cause for concern in healthcare systems throughout the world.

The recently issued Infectious Diseases Society of America clinical practice guidelines [4] recommend vancomycin or daptomycin for the treatment of bacteremia and native valve IE caused by MRSA. Vancomycin has been the first choice against invasive MRSA infections for decades, even though its bactericidal activity...
against *S. aureus* is poorer than that of betalactams [5] and its penetration in the endocardial vegetations is diminished [6]. Therefore, its suitability against invasive MRSA infections has been the subject of debate [7], and different antibiotic regimens have been assessed during recent years. Daptomycin is considered a reliable alternative for severe MRSA infections based on the results of several in vitro and in vivo studies that showed rapid bactericidal activity against both exponential-phase and stationary-phase bacteria [8]. However, the shortcomings of the drug include its profound inoculum effect and significant binding to plasma proteins, which may affect efficacy in clinical practice [9]. The only randomized trial that compared these 2 antibiotics included 88 episodes of MRSA bloodstream infection [10]. Success rates with daptomycin at 6 mg/kg and vancomycin (alone or with gentamicin) at standard doses were 44.4% and 32.6% (95% confidence interval [CI], –8.3 to 32.1). In addition, in left-side IE episodes, success rates decreased to 11.1% for daptomycin and 22.2% for vancomycin. Notably, resistance to daptomycin emerged in 6 of 19 episodes (32%) with microbiological failure, most of which were deep-seated infections (eg, cardiovascular infections, bone and joint infections, and nondrained abscesses). This clinical scenario highlights the need for alternative rescue therapies against MRSA bacteremia and IE.

Fosfomycin has been used in clinical practice for many years. It has rapid bactericidal activity against gram-positive and gram-negative microorganisms by inhibiting uridine diphosphate-N-acetylmuramyl-l-alanine enolpyruvyl transferase, which is essential in the early stages of peptidoglycan synthesis [11]. As this unique mechanism of action makes cross-resistance highly unusual, fosfomycin retains activity against most MRSA strains [12]. However, when used in monotherapy, selection of resistant mutants is the rule [13], with the result that combination with other agents is necessary when treating severe infections.

Many in vitro and in vivo studies have reported the efficacy of combinations of fosfomycin and betalactams against *S. aureus* [14–19]. Specifically, imipenem has shown synergism with fosfomycin against numerous *S. aureus* and MRSA strains [20, 21]. Our group also described the efficacy of this combination in experimental MRSA IE (conference abstract, not published) [22]. It has been suggested that synergy between these antibiotics against MRSA is associated with changes in the proportion of specific membrane penicillin-binding proteins (PBPs) induced by fosfomycin, specifically PBP2a in the MRSA membrane, which can repress, leading strains to regain their susceptibility to betalactams [19]. During the 1980s, fosfomycin plus cefotaxime was successfully used as therapy for bacteremia, meningitis, and acute osteoarthitis caused by MRSA and methicillin-resistant *Staphylococcus epidermidis* [23–25]. Furthermore, when combined with other antibiotics such as daptomycin, aminoglycosides, or vancomycin, fosfomycin showed good results against invasive MRSA infections [26, 27]. We performed a clinical trial to describe the efficacy and safety of fosfomycin plus imipenem as rescue therapy in 16 patients with MRSA bloodstream infections in whom vancomycin or daptomycin had failed.

**METHODS**

**Study Design**

At the 3 teaching centers that participated in the study, MRSA bacteremia episodes identified by the microbiology laboratory were prospectively monitored by an infectious diseases specialist, who provided advice about the appropriate diagnostic and therapeutic procedures in each clinical situation, including the early resolution of the focus of infection when feasible. The patients eligible for the study were adults receiving appropriate antibiotic therapy for MRSA bacteremia or IE but who needed rescue therapy because of persistent bacteremia, unacceptable side effects of antibiotics, or relapse. After signing the informed consent, the patients who were enrolled in the study were treated with fosfomycin (2 g/6 hours IV) plus imipenem (1 g/6 hours IV). Doses of both antibiotics were adjusted in patients with creatinine clearance ≤60 mL/min. The 3 local institutional review boards approved the study.

**Definitions**

MRSA bacteremia was defined as the presence of at least 1 positive MRSA blood culture in a sample from a patient with clinical findings consistent with infection. For the diagnosis of IE and prosthetic vascular graft infection, we applied the modified Duke criteria [28] and Fitzgerald criteria [29], respectively. Episodes that yielded MRSA in blood cultures for 6 days or more despite appropriate antibiotic therapy were defined as persistent bacteremia, and those yielding MRSA within 4 weeks after the end of therapy were defined as relapse. Source of bacteremia was defined according to Centers for Disease Control and Prevention criteria [30]. Three acquisition categories were established following the Friedman criteria: (i) nosocomial if the episode was diagnosed at least 48 hours after admission to a hospital ward and there were no signs or symptoms of infection at admission; (ii) healthcare-related acquisition if it was diagnosed within 48 hours of admission and if signs or symptoms consistent with the infection developed before hospitalization in patients with extensive out-of-hospital contact with healthcare interventions or systems, defined as receipt of intravenous therapy, wound care, or specialized nursing care at home within the 30 days before onset of the episode; receipt of hemodialysis or intravenous chemotherapy in the 30 days before the onset of the episode; hospitalization for 2 or more days in the 90 days before the onset of the episode; or residence in a nursing home or long-term care facility; and (iii) community acquisition if the episode did not fit the previous conditions [31].
Initial antibiotic treatment was considered appropriate if the regimen included either vancomycin at doses adjusted to achieve minimum trough serum levels of 10–15 µg/mL or daptomycin at ≥6 mg/kg.

**Treatment and Monitoring**
Clinical management was based on the criteria of the infectious diseases specialist and standard recommendations [8]. Between 2001 and 2005, all patients received vancomycin as initial therapy; this was continued, and fosfomycin plus imipenem was added. After 2006, fosfomycin plus imipenem was administered instead of the initial antibiotic regimen, which included either daptomycin at 6–10 mg/kg or vancomycin. Blood cultures were obtained every 72 hours until growth of MRSA was no longer observed. All patients were evaluated, including with blood cultures, at baseline (enrollment), the end of therapy, 14 days after the end of therapy, and at the test-of-cure visit (45 days after the end of therapy).

**Clinical Outcomes**
The primary efficacy endpoints were the percentage of sterile blood cultures at 72 hours and the clinical success rate assessed at the test-of-cure visit in the intention-to-treat population. Treatment was classified as clinically successful when the patient was alive, lacked signs or symptoms of infection, and had sterile blood cultures at the test-of-cure visit. Failure was defined as death, positive blood cultures, or discontinuation of fosfomycin plus imipenem because of persistent bacteremia or adverse events. The safety endpoint was the frequency of adverse events assessed at the test-of-cure visit.

**Microbiological Methods**
*Staphylococcus aureus* were identified using latex agglutination (Pastorex Staph-plus, Bio-Rad Laboratories, Madrid, Spain) and DNase production (DNAs E-test Agar, bioMérieux, Marcy l’Étoile, France). Methicillin resistance was identified using direct polymerase chain reaction (PCR) of the mecA gene (GeneXpert; Cepheid AB, Solna, Sweden) and/or PCR of PBP2a by latex agglutination (Denka Seiken, Nigata, Japan). The antimicrobial susceptibility of all MRSA isolates was tested in a central laboratory using the disk-diffusion method, E-test, and microdilution method according to Clinical and Laboratory Standards Institute recommendations [32].

**Statistical Analysis**
Efficacy and safety outcomes in the intention-to-treat population analysis were calculated with 95% CIs. Patient survival was analyzed by taking the date of treatment with fosfomycin plus imipenem as the start date. Survival time from the treatment with fosfomycin plus imipenem was estimated using the Kaplan–Meier product-limit method. Analyses were performed using SPSS version 21 (Microsoft, Redmond, WA).

**RESULTS**

**Patients**
Twelve of the 16 patients enrolled in the study were diagnosed with IE, 2 with vascular graft infection and 2 with complicated bacteremia. Their main clinical characteristics are summarized in Table 1. Median patient age was 67.5 years (range, 25–87); 13 patients (81%) had previous chronic comorbid conditions. Although the patients had received appropriate antibiotic therapy for a median of 9.5 days (range, 6–30), MRSA was still detected in the blood cultures of 14 patients. The other 2 patients were diagnosed with relapse, both 14 days after the end of appropriate antibiotic therapy. The median (interquartile range [IQR]) vancomycin trough level before switching either to a second drug or to fosfomycin plus imipenem was 18.1 µg/mL (range, 11.3–19.8).

**MRSA Isolates**
All MRSA isolates were susceptible to vancomycin and daptomycin; the median vancomycin minimum inhibitory concentration (MIC) was 1 µg/mL (range, 1–2), while the median daptomycin MIC was 0.25 µg/mL (range, 0.094–0.5). The fosfomycin MIC of all isolates except 1 (episode 1) was <32 µg/mL, and 4 isolates (episodes 3, 12, 14, and 16) had imipenem MICs within the susceptible range.

**Treatment and Outcomes**
As a whole, fosfomycin plus imipenem was administered for a median of 28 days (range, 4–75) as rescue therapy. In all cases, blood cultures were negative 72 hours after the first dose. Median time to clearance from the first dose of appropriate antibiotic therapy was 12 days (IQR, 9.5–22.5). Breakthrough episodes of MRSA bacteremia were not observed after the initiation of fosfomycin plus imipenem. At the test-of-cure visit, 11 patients were cured and 5 (31%) had died; 2 died during antibiotic treatment and 3 died after finishing treatment, all with sterile blood cultures at 14 days after the end of therapy. In 4 of the 5 deaths, the cause was not directly related to the infection or to the antibiotic therapy. The fifth patient died because of multiorgan failure related to sodium overload (see below). Two patients with IE underwent cardiac surgery (patients 1 and 2) because of congestive heart failure. In both cases, the cultures of the valve vegetations were negative. Both patients were considered cured after 12 months of follow-up. The mortality rate of patients diagnosed with IE was 25%. Overall survival (95% CI) at 90 days was 69% (46 to 91). No relapses were diagnosed within the follow-up period after therapy.

Side effects attributable to the antibiotic combination were observed in 5 patients. Leucopenia and fungal bloodstream infection were diagnosed in 1 patient each, while 3 patients with liver cirrhosis had sodium overload that required more frequent
Table 1. Summary of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection Episodes Treated With Fosfomycin Plus Imipenem as Rescue Therapy

<table>
<thead>
<tr>
<th>Episode Characteristics</th>
<th>Therapy and Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No.</td>
<td>Year</td>
</tr>
<tr>
<td>1</td>
<td>2001</td>
</tr>
<tr>
<td>2</td>
<td>2003</td>
</tr>
<tr>
<td>3</td>
<td>2004</td>
</tr>
<tr>
<td>4</td>
<td>2005</td>
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<tr>
<td>5</td>
<td>2006</td>
</tr>
<tr>
<td>6</td>
<td>2006</td>
</tr>
<tr>
<td>7</td>
<td>2006</td>
</tr>
<tr>
<td>8</td>
<td>2007</td>
</tr>
<tr>
<td>9</td>
<td>2008</td>
</tr>
</tbody>
</table>
Table 1 continued.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Year</th>
<th>Age/Gender</th>
<th>Comorbid Conditions</th>
<th>Source</th>
<th>Diagnosis</th>
<th>Therapy and Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2009</td>
<td>65/M</td>
<td>Heart failure</td>
<td>Vascular catheter</td>
<td>Mi+Ao PV IE</td>
<td>DAP ≤1 21 42 Sterile Leucopenia Cured</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Leucopenia was attributed to imipenem; antibiotic did not have to be withdrawn; DAP was switched to FOSIMI because of persistent bacteremia</td>
</tr>
<tr>
<td>11</td>
<td>2010</td>
<td>31/M</td>
<td>HIV IV drug user</td>
<td>Skin</td>
<td>Community Ao NV IE</td>
<td>VAN NA 6 28 Sterile No Cured</td>
</tr>
<tr>
<td>12</td>
<td>2010</td>
<td>81/M</td>
<td>Lymphoma, heart failure</td>
<td>Vascular catheter</td>
<td>Mi+Ao PV IE + mediastinitis</td>
<td>DAP ≤1 6 31 Sterile No Not cured</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Admitted to perform annuloplasty for severe mitral regurgitation and moderate aortic insufficiency; early complications included acute myocardial infarction, complete atrioventricular block, and heart failure; death 31 d after the first dose of FOSIMI because of heart failure</td>
</tr>
</tbody>
</table>

Episodes of Vascular Graft Infections

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Year</th>
<th>Age/Gender</th>
<th>Comorbid Conditions</th>
<th>Source</th>
<th>Diagnosis</th>
<th>Therapy and Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>2002</td>
<td>60/F</td>
<td>Diabetes, chronic renal disease</td>
<td>Deep Surgical infection</td>
<td>Nosocomial Vascular graft infection</td>
<td>VAN, TEI Not performed 6 39 Sterile No Cured</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VAN was switched to TEI after 2 d because of ARF; TEI was switched to FOSIMI because of persistent bacteremia</td>
</tr>
<tr>
<td>14</td>
<td>2003</td>
<td>69/F</td>
<td>Liver cirrhosis (Child Pugh C), diabetes</td>
<td>Unknown HCR</td>
<td>TIPS infection</td>
<td>VAN, TEI, LIN TIPS not removed 22 4 Sterile Sodium overload Not cured</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VAN was switched to TEI after 7 d because of ARF; TEI and LIN were switched to FOSIMI because of persisten bacteremia; death 4 d after the first dose of FOSIMI, with previous negative blood cultures at 72 h; cause of death was hypernatremia and ARF</td>
</tr>
</tbody>
</table>

Episodes of Complicated Bacteremia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Year</th>
<th>Age/Gender</th>
<th>Comorbid Conditions</th>
<th>Source</th>
<th>Diagnosis</th>
<th>Therapy and Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>2009</td>
<td>74/F</td>
<td>Lymphoma, chemotherapy</td>
<td>Unknown HCR</td>
<td>Spondylitis, persistent bacteremia</td>
<td>VAN, DAP NA 30 31 Sterile No Cured</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DAP was switched to FOSIMI because of persistent bacteremia</td>
</tr>
</tbody>
</table>
paracentesis. One of these 3 patients died of hypernatremia, metabolic acidosis, and acute renal failure (episode 14). Antibiotics did not have to be withdrawn in any of the remaining 15 patients.

**DISCUSSION**

MRSA bloodstream infections are associated with high mortality rates, which have not significantly decreased with extended use of new antibiotics, more in-depth knowledge of infection, and advances in medical support during recent decades [33]. As a result, these infections remain challenging and difficult to treat.

The availability of alternative rescue antibiotics is critical for improving the poor outcome of these infections. In recent years, agents such as ceftaroline [34] and daptomycin combined with beta-lactams [35] or fosfomycin [27] have been tested in clinical trials. In the present study, we found fosfomycin plus imipenem administered as rescue therapy to be safe and effective for treatment of MRSA bloodstream infections.

Since the first report of an invasive MRSA infection treated with fosfomycin plus beta-lactams in 1989 [23], few other experiences have been reported [24], although outcome was favorable in most of the cases reported, as we found in our study. Our most notable result was the short time to cure (100% of cases), which was verified with sterile blood cultures 72 hours after the first combination dose. This finding is highly relevant, since the presence of persistent positive blood cultures in left-sided IE has recently been identified as an independent risk factor for in-hospital mortality [36]. For decades, time to clearance of MRSA bacteremia has been thought to be close to 7 days [37]. In a recent clinical trial comparing daptomycin with standard antibiotic therapy, the median time to clearance of MRSA bacteremia was more than 8 days for both strategies [10].

Although mortality rates in our study remained high, they were lower than those reported elsewhere, especially in IE, where they are around 30%–40% [3, 10].

Based on our experience, sodium overload was the most remarkable side effect and the only one that was eventually associated with death (1 patient). Consequently, water balance and plasma osmolarity in patients with liver cirrhosis receiving fosfomycin should be closely monitored in order to minimize associated morbidity. In contrast, we did not observe other side effects previously associated with fosfomycin (eg, hypokalemia or injection-site reactions) [38]. No patients presented imipenem-induced seizures. More studies should be performed to assess the prevalence and clinical relevance of the side effects attributed to fosfomycin.

The specific antibiotics and doses used in this study were based on the rationale of combining therapies for difficult-to-treat infections. First, the combination of fosfomycin and imipenem had previously shown in vitro synergism against *S. aureus* and MRSA [12, 14–16, 22]. The second reason for
using the combined regimen was the prevention of resistance to fosfomycin, which precludes monotherapy [39]. Last, the possibility of administering smaller doses of antibiotics to limit associated side effects is a key advantage of combined regimens. Since the recommended daily dose of intravenous fosfomycin is 8–16 g, the amount of sodium administered can range from 2.6 to 5.3 g per day (1 g of fosfomycin brings 330 mg [14.4 mL] of sodium). Taking advantage of the association with imipenem, we used the lower dose of fosfomycin to minimize sodium overload, which could prove deleterious in patients with cardiac insufficiency, renal failure, or liver cirrhosis, as we observed.

Our study was limited by the small number of patients enrolled and the heterogeneity of the initial antibiotic regimens administered before the first doses of fosfomycin plus imipenem. Furthermore, we must take into consideration the potential impact of previous antibiotic therapy on final outcome and the possibility of treatment selection bias. Therefore, our results should be interpreted with caution. However, our findings do provide evidence of the efficacy and safety profile of fosfomycin plus imipenem as rescue therapy for MRSA bloodstream infections, which is also being assessed in an ongoing randomized clinical trial comparing fosfomycin plus imipenem with vancomycin for endocarditis caused by MRSA isolates with vancomycin MIC < 2 µg/mL (ClinicalTrials.gov Identifier: NCT00871104).

Notes

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Potential conflicts of interest. J. M. M. has received consulting honoraria and/or research grants from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Cubist, Novartis, Glaxo Smith Kline, Gilead Sciences, Pfizer, Roche, and Theravance. F. M. has received consulting honoraria from Novartis and Jansen-Cilag. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


APPENDIX
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