Comparative Efficacies of Amoxicillin, Clindamycin, and Moxifloxacin in Prevention of Bacteremia following Dental Extractions


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We evaluated the efficacies of oral prophylactic treatment with amoxicillin (AMX), clindamycin (CLI), and moxifloxacin (MXF) in the prevention of bacteremia following dental extractions (BDE). Two hundred twenty-one adults who required dental extractions under general anesthesia were randomly assigned to a control group, an AMX group, a CLI group, and an MXF group (the individuals in the drug treatment groups received 2 g, 600 mg, and 400 mg, respectively, 1 to 2 h before anesthesia induction). Venous blood samples were collected from each patient at the baseline and 30 s, 15 min, and 1 h after the dental extractions. The samples were inoculated into BACTEC Plus aerobic and anaerobic blood culture bottles and were processed in a BACTEC 9240 instrument. Subculture and the further identification of the isolated bacteria were performed by conventional microbiological techniques. The prevalences of BDE in the control group, AMX group, CLI group, and MXF group were 96, 46, 85, and 57%, respectively, at 30 s; 64, 11, 70, and 24%, respectively, at 15 min; and 20, 4, 22, and 7%, respectively, at 1 h. Streptococcus spp. were the most frequently identified bacteria in all groups (44 to 68%), with the lowest percentage being detected in the AMX group (44%). AMX and MXF prophylaxis showed high efficacies in reducing the prevalence and duration of BDE, but CLI prophylaxis was non-effective. As a consequence, MXF prophylaxis is a promising antibiotic alternative for the prevention of BDE when beta-lactams are not indicated.

The controversy over bacterial endocarditis (BE) of oral origin has intensified during the past decade, based principally on estimates of the incidence (18) and on case-control studies which exclude dental treatment as a risk factor (45). Concerning bacteremia following dental manipulations, the small size of the bacterial inoculum, its transient nature, and the concept of cumulative exposure associated with “everyday” events have also been discussed (34). As a consequence, Durack (12) suggested that the indications for the administration of antibiotic prophylaxis (AP) for BE should be restricted. Furthermore, as there is no evidence of the efficacy of AP for the prevention of BE related to dental manipulations in patients “at risk” (31), some experts are starting to question whether the routine use of AP is necessary and whether the guidelines should be updated (32). However, the use of AP in patients “at risk” of BE who undergo “at-risk” dental procedures is a relatively widely accepted practice (48).

In accordance with the latest AP guidelines drawn up by expert committees, amoxicillin (AMX) continues to be the antibiotic of choice for patients “at risk” of BE and who are to undergo certain dental procedures; for patients allergic or intolerant to penicillin (PEN), the antibiotic of choice is clindamycin (CLI) (3, 9, 20).

The effect of CLI prophylaxis on the prevention of bacteremia following dental procedures has been evaluated in very few studies, and the results of those studies do not confirm the efficacy of CLI (1, 17, 19). Moreover, increasing resistance to CLI among streptococci isolated from the bloodstream after dental extractions has been found (47); this could limit its use as a prophylactic drug.

Moxifloxacin (MXF) is a broad-spectrum antibacterial agent approved for use for the treatment of acute exacerbations of chronic bronchitis, community-acquired pneumonia, acute bacterial sinusitis, and uncomplicated skin and skin structure infections (22). This fluoroquinolone shows good in vitro activity against odontogenic pathogens (23, 27, 43). Recently, we have found that all the streptococci isolated from a series of patients with iatrogenic bacteremia of oral origin showed a low MIC to MXF (47). Furthermore, we have demonstrated its efficacy in vivo for the treatment of submucous layer dental abscesses, confirming its penetration into tissue in the oral cavity (24).

The objective of this prospective, double-blind, randomized study was to investigate the efficacies of the prophylactic administration of AMX, CLI, and MXF for the prevention of bacteremia following dental extractions (BDE).

MATERIALS AND METHODS

Selection of study group. The study group comprised patients who, for behavioral reasons (autism, learning disabilities, phobias, etc.), underwent dental extractions under general anesthesia in the Santiago de Compostela University Hospital (Santiago de Compostela, Spain) from January 2003 to December 2004.

The following exclusion criteria were applied: age under 18 years; receipt of antibiotics in the previous 3 months; routine use of oral antiseptics; a history of allergy or intolerance to AMX, CLI, or MXF; any type of congenital or acquired immunodeficiency; or any known risk factor for BE. By applying these criteria, 221 patients were selected and were randomly distributed into four study groups:
the control group comprised 53 patients who did not receive any type of prophylaxis before the surgical procedure; the AMX group comprised 56 patients who received a standard prophylactic regimen of 600 mg of CLI (Dalicur: Upjohn Farmaquímica, Madrid, Spain) orally 1 to 2 h before anesthesia induction; the CLI group comprised 54 patients who received a standard prophylactic regimen of 400 mg of MXF (Actira; Química Farmacéutica Bayer, Barcelona, Spain) orally 1 to 2 h before anesthesia induction; and the MXF group comprised 58 patients who received a prophylactic regimen of 400 mg of MXF (Actira; Química Farmacéutica Bayer, Barcelona, Spain) orally 1 to 2 h before anesthesia induction.

Randomization was based on a single sequence of random assignments (simple randomization) by application of a computer-generated randomization list. This project was approved by the Ethics Committee of the Faculty of Medicine and Dentistry of the University of Santiago de Compostela; in all cases, informed consent was obtained from the patients or from their legal representatives before their participation in the study.

### Determination of oral health status
After the age and sex of each patient were recorded, the oral health grade was established for each patient by using a previously validated, specifically designed scale which incorporated criteria of dental and periodontal health (11). The oral health grades established were between grade 0 (healthy mouth) and grade 3 (neglected mouth).

### Collection of samples for blood culture
To determine the prevalence of BDE, a peripheral venous blood sample (10 ml) was drawn from each patient at the baseline (before the dental manipulation was performed but after nasotracheal intubation) and 30 s, 15 min, and 1 h after the final dental extraction. For the collection of blood for culture, a large-bore (18- to 22-gauge) angiocath needle was placed in a puncture site in the antecubital fossa or dorsum of the hand, after the site was scrubbed in the usual manner with alcohol and then with povidoneiodine. The angiocath needle and line were flushed with 3 ml of saline after each blood drawn, and 2 ml of blood was drawn and discarded just before each blood sample was drawn. Each blood sample was equally divided and placed into two bottles with aerobic and anaerobic culture media, respectively (BACTEC Plus; Becton Dickinson and Company, Sparks, MD) and immediately transported to the laboratory. The collection, handling, and transport of the blood samples for blood culture were performed according to the recommendations of the Spanish Society of Infectious Diseases and Clinical Microbiology (37).

### Microbiological analysis of blood cultures
In the laboratory, a total of 829 pairs of blood culture bottles were processed in a BACTEC 9240 instrument (Becton Dickinson): 209 for the control group, 206 for the AMX group, 202 for the CLI group, and 212 for the MXF group. A Gram stain was performed on each positive blood culture. The positive blood cultures in the aerobic media were subcultured on blood agar and chocolate agar in an atmosphere of 5 to 10% CO2 and on MacConkey agar under aerobic conditions. The same protocol was used for the positive blood cultures in the anaerobic media, with subculture on Schaedler agar and incubation in an anaerobic atmosphere. The bacteria isolated were identified by using the battery of biochemical tests provided with the Vitek system (bioMe´rieux Inc., Hazelwood, MO) for gram-positive bacteria, _Neisseria_ spp., _Haemophilus_ spp., and _Streptococcus_ group streptococci were classified into five groups, the _Streptococcus mitis, S. anginosus, S. salivarius, S. mutans_, and _S. sanguinis_ groups, by applying the Ruoff criteria (38, 39). Facklam’s criteria (14) were used to identify unusual _Streptococcus_ spp. and other gram-positive cocci in chains.

### Sensitivity to antibiotics
The MIC was determined by the Etest (AB Biodisk, Solna, Sweden) on Mueller-Hinton agar medium supplemented with 5% horse blood and incubation in 5% CO2 (for aerobes, _Streptococcus_ spp., and other facultative anaerobes) and on brucella agar medium supplemented with vitamin K and hemin with incubation in an anaerobic atmosphere (for obligate anaerobes). The readings were made according to the manufacturer’s recommendations. The criteria of the Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) were applied for the qualitative interpretation of the MICs for _Streptococcus_ spp. and obligate anaerobic bacteria (29, 30). The antibiotics evaluated were PEN, AMX, ampicillin (AMP), erythromycin (EM), CLI, and MXF. The control microorganisms used were _Streptococcus pneumoniae_ ATCC 49619 and _Bacteroides fragilis_ ATCC 25285.

### Statistical analysis
The results were analyzed by using the SPSS (version 12.0) statistical package for Windows (SPSS Inc., Chicago, IL). Analysis of variance and the Kruskal-Wallis test were used to compare the ages of the patients in the different study groups and the number of dental extractions performed between the different study groups, respectively. The chi-square test was used to compare the genders and the oral health grades between the different study groups. Fisher’s exact test was used to compare the prevalence of bacteremia at the different study groups.
baseline and 30 s, 15 min, and 1 h after completion of the dental extractions; the percentage of positive blood cultures; and the frequency of polymicrobial blood cultures between the different study groups. The Mann-Whitney U statistic was used to compare the MICs of AMX, CLI, and MXF for all strains isolated in the different study groups. A P value of <0.05 was considered statistically significant.

The power of the study was calculated by comparing the “prevalence of bacteremia” obtained at 30 s after the dental extractions between a preliminary control group (n = 14) and a preliminary AMX group (n = 12), CLI group (n = 15), and MXF group (n = 12). The prevalence of bacteremia in this control group was 93%, that in the AMX group was 58% (statistical power, 0.6; estimated sample size, 21), that in the CLI group was 87% (statistical power, 0.08; estimated sample size, 392), and that in the MXF group was 42% (statistical power, 0.8; estimated sample size, 11).

RESULTS

Characteristics of study group.

The study group was made up of 221 patients, including 126 (57%) males and 95 (43%) females, with a mean age of 24.9 ± 5.7 years (age range, 18 to 57 years). With regard to the oral health scale, 46 patients (21%) belonged to grades 0 and 1, 84 (38%) to grade 2, and 91 (41%) to grade 3. The median number of teeth extracted per patient was 4 (interquartile range, 6). No significant differences were found between the different study groups with regard to age, sex, oral health grade, or number of teeth extracted (Table 1).

Prevalence of bacteremia.

At the baseline, the percentages of positive blood cultures detected were 9.4% in the control group, 5% in the AMX group, 12.5% in the CLI group, and 7.5% in the MXF group.

The prevalence of bacteremia at 30 s after completion of the final dental extraction was 96.2% in the control group. In comparison with the control group, this percentage was significantly lower in the AMX group (46.4%; P < 0.001) and in the MXF group (56.9%; P < 0.001) but not in the CLI group (85.1%; P < 0.1). The administration of AMX and MXF showed efficiencies significantly superior to those achieved in the patients administered CLI (P < 0.001 and P ≤ 0.001, respectively) (Fig. 1).

The prevalence of bacteremia at 1 h after completion of the final dental extraction was 64.2% in the control group. In comparison with the control group, this percentage was significantly lower in the AMX group (10.7%; P < 0.001) and in the CLI group (24.1%; P < 0.001) but not in the CLI group (70.6%; P < 0.6). The administration of AMX and MXF showed efficiencies significantly superior to those achieved in the patients administered CLI (P < 0.001 and P < 0.001, respectively) (Fig. 1).

The prevalence of bacteremia at 15 min after the completion of the final dental extraction was 20% in the control group. In comparison with the control group, this percentage was significantly lower in the AMX group (10.7%; P < 0.001) and in the MXF group (24.1%; P < 0.001) but not in the CLI group (70.6%; P < 0.6). The administration of AMX and MXF showed efficiencies significantly superior to those achieved in the patients administered CLI (P < 0.001 and P < 0.001, respectively) (Fig. 1).

Characteristics and identification of bacterial isolates. Statistically significant differences were observed in the percentages of positive blood cultures between the control group and the AMX and MXF groups (47.8 versus 17.5 and 25.5%, respectively; P < 0.001) but not the CLI group (47.8% and 50%, respectively; P < 0.5). Statistically significant differences were also observed in the proportion of polymicrobial blood cultures between the control group and the AMX group (29 and
The bacteria that were the most frequently isolated from all the study groups were the anaerobic bacteria (facultative and obligate anaerobes); the percentages of facultative anaerobes varied between 66.7% in the AMX group and 83.9% in the MXF group; the percentages of obligate anaerobes varied between 9.8% in the control group and 22.2% in the AMX group. Gram-positive cocci were the most frequently observed bacteria in all the study groups; the lowest prevalence occurred in the AMX group (66.7%), and the highest occurred in the MXF group (80.6%). The highest percentage of gram-negative bacilli was observed in the AMX group (27.8% versus 6.4% to 8.8% in the other groups).

The most frequent bacterial genus in the positive blood cultures in the control group was *Streptococcus* (63.1%, particularly the viridans group), followed by the genera *Staphylococcus* (11.3%) and *Neisseria* (7.5%). In the AMX group, the most frequent bacterial isolates were viridans group streptococci (44.4%), all of which belonged to the *S. mitis* group, followed by obligate anaerobes, such as *Peptostreptococcus* spp. (11.1%) and *Prevotella* spp. (11.1%). In the CLI group, the most frequent bacterial genus was *Streptococcus* (58.5%), particularly the viridans group, followed by the genera *Neisseria* (14.8%) and *Prevotella* (5.9%). In the MXF group, the most frequent isolates were viridans group streptococci (67.7%), followed by *Staphylococcus* spp. (9.7%) and obligately anaerobic bacteria (9.7%). The genera, groups, and, where indicated, species of bacteria identified in all the study groups are shown in Table 2.

**Antimicrobial sensitivities of bacteria isolated in postextraction blood cultures.** The profiles of sensitivity to the beta-lactams (PEN, AMP, AMX), EM, CLI, and MXF were studied for 177 bacterial strains derived from the positive postextraction blood cultures (62 isolates from the control group, 24 from the AMX group, 66 from the CLI group, and 25 from the MXF group). The MIC₉₀ of PEN for the isolates was 2 mg/liter, and the MIC₉₀ of AMP and AMX were 1 mg/liter. The MIC₉₀ of EM and CLI were ≥256 mg/liter. The MIC₉₀ of MXF for the isolates was 0.19 mg/liter. Figure 2 shows the percentage of cumulative MICs of AMX, CLI, and MXF for all strains isolated from the different study groups. The MIC₉₀ of AMX for the isolates from the control group and the AMX group were 0.75 mg/liter and 4 mg/liter, respectively, with this difference being statistically significant (*P* < 0.005). The MIC₉₀ of CLI for the isolates from the control group and the CLI group were ≥256 mg/liter. The MIC₉₀ of MXF for the isolates from the control group and the MXF group were 0.125 mg/liter and 0.380 mg/liter, respectively. Table 3 shows the MICs and the antimicrobial sensitivity profiles of the *Streptococcus* spp. (133 isolates), obligate anaerobic bacteria (20 isolates), and other bacteria (24 isolates) isolated in the postextraction blood cultures, irrespective of the study group from which they were isolated.

FIG. 2. Percentage of cumulative MICs of amoxicillin, clindamycin, and moxifloxacin for all strains isolated from the control group (62 isolates), amoxicillin group (24 isolates), clindamycin group (66 isolates), and moxifloxacin group (25 isolates).
recovered. Only 1.5%, 0.8%, and 0.8% of the *Streptococcus* spp. were highly resistant to PEN, AMP, and AMX, respectively; 45.9% and 22.6% of the *Streptococcus* spp. showed high levels of resistance to EM and CLI, respectively; and 45% of the obligate anaerobes were highly resistant to PEN, 30% were highly resistant to AMP, and 20% were highly resistant to AMX. The MIC₉₀ of MXF for *Streptococcus* spp., obligate anaerobic bacteria, and other bacteria were 0.19 mg/liter, 0.19 mg/liter, and 0.5 mg/liter, respectively.

**DISCUSSION**

The efficacy of AMX for the prevention of bacteremia after dental manipulations has been demonstrated both in children and in adults (25, 41, 49). Recently, Lockhart et al. (25) found that AMX prophylaxis also reduced the duration of BDE in a group of children undergoing dental treatment while they were under general anesthesia, as all the cultures of blood collected from the AMX group at 30 and 45 min after completion of the final dental extraction were negative (0% versus 16% and 14% from the AMX group at 30 and 45 min after completion of the extraction). In the present series, AMX prophylaxis also significantly reduced the frequencies of BDE in both groups; the frequencies of BDE after extraction of the third molar from patients receiving CLI prophylaxis and from patients in a control group; the prevalence of positive blood cultures for the controls, respectively). In the present series, CLI prophylaxis did not reduce the prevalence of BDE.

In some current protocols for BE prophylaxis, the administration of macrolide antibiotics such as azithromycin and clarithromycin has been proposed as the second choice for PEN-allergic patients “at risk” of BE before certain dental manipulations (10, 42). Aitken et al. (1) suggested that CLI was more effective than EM in reducing the prevalence of BDE of streptococcal etiology; but other authors, such as Hall et al. (19), did not detect significant differences between the two AP regimens. In the literature we have only found one report, published by Gökçen and Güvenen (17) in 1992, which compared the prevalence of positive blood cultures after extraction of the third molar from patients receiving CLI prophylaxis and from patients in a control group; the frequencies of BDE in both groups were similar. In the present series, CLI prophylaxis did not reduce the prevalence or the duration of BDE.

In agreement with the results obtained in previous studies (5), AMX prophylaxis showed a “selective effect” on *Streptococcus* spp., with a marked reduction in their prevalence in the positive postextraction blood cultures in our series, in which all the streptococci in the AMX group belonged to the *S. mitis* group. Since 1990, due to the high prevalence of undesirable gastrointestinal effects caused by EM, the expert committees of BE recommend the administration of CLI as the prophylactic alternative in PEN-allergic patients “at risk” of BE before certain dental manipulations (10, 42). However, authors such as Hall et al. (19), did not detect significant differences between the two AP regimens. In the literature we have only found one report, published by Gökçen and Güvenen (17) in 1992, which compared the prevalence of positive blood cultures after extraction of the third molar from patients receiving CLI prophylaxis and from patients in a control group; the frequencies of BDE in both groups were similar. In the present series, CLI prophylaxis did not reduce the prevalence or the duration of BDE.

TABLE 3. MIC₉₀, MIC₉₀, MIC ranges, and profiles of sensitivities to beta-lactams, erythromycin, clindamycin, and moxifloxacin for the bacteria isolated in the postextraction blood cultures

<table>
<thead>
<tr>
<th>Bacteria and antibiotic</th>
<th>MIC (mg/liter)</th>
<th>% of isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td><em>Streptococcus</em> spp. (n = 133 isolates)⁹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.032</td>
<td>0.5</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0.064</td>
<td>0.5</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.676</td>
<td>0.5</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.064</td>
<td>0.19</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.064</td>
<td>0.19</td>
</tr>
<tr>
<td>Obligate anaerobic bacteria (n = 20 isolates)²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.5</td>
<td>32</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0.125</td>
<td>≥256</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>2.3</td>
<td>≥256</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.064</td>
<td>0.19</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.064</td>
<td>0.19</td>
</tr>
<tr>
<td>Other bacteria (n = 24 isolates)³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.064</td>
<td>0.19</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.094</td>
<td>0.5</td>
</tr>
</tbody>
</table>

¹ A total of 177 isolates were tested. Abbreviations: S, sensitive; IR, intermediate resistance; HR, high-level resistance; NA, not applicable.
² The CLSI criteria were applied to perform the qualitative interpretation (29, 30).
³ The qualitative interpretation of the MICs was not performed due to the low number of microorganisms of some of the bacterial genera identified and the lack of specific CLSI criteria for some of these isolates.
tion blood cultures in the present series, the efficacy of azithromycin in the prevention of BDE could be questioned.

MXF has shown good in vitro activity against both oral streptococci (macrolide-sensitive or -resistant) and anaerobic pathogens (23, 27, 43, 47). Recently, we have found in a series of BDE that all the streptococci isolated showed a low MIC to MXF (47). Furthermore, the properties of MXF are favorable both pharmacokinetically (high bioavailability, long half-life, and good tissue penetration) and pharmacodynamically (MXF is bactericidal at concentrations two- to fourfold higher than the MIC) (26). The most common drug-related adverse effects involve the gastrointestinal tract and the central nervous system and were usually transient and mild in severity (4). Its lack of significant drug interactions in target groups makes it an option in diabetic patients and elderly individuals, as well as in those with renal dysfunction or with mild to moderate hepatic impairment (4). MXF appears to be tolerated by patients with hypersensitivity reactions to beta-lactam antibiotics (7). Although all these arguments would justify clinical trials with this antibiotic, to our knowledge no studies in which the effect of MXF on the prevention of bacteremia following dental manipulations has been investigated have been published to date. In the present series, the administration of a single oral dose of 400 mg of MXF leads to a significant reduction in the prevalence and duration of BDE.

The effect of AP in the bloodstream in the first minutes after the onset of a bacteremic episode has been questioned, since the time of exposure of the bacteria to the antibiotic is probably insufficient for the antibiotic to act (16, 19). In view of this, some authors (1, 6) have suggested that the success of AP in the prevention of postdental manipulation bacteremia could be attributed to the local effect of the drug on the bacteria in the oral cavity, before these invade the bloodstream. In accordance with the findings of other authors (25, 35), in our study, the administration of the antibiotic was performed 1 to 2 h after anesthesia induction, signifying that at least 2 h passed before the administration of therapeutic doses (2, 15, 28, 44), 90% of the bacteria in the present series would be sensitive to the activities of AMX and MXF. However, in our series, the MIC\textsubscript{90} of CLI was much higher than the concentrations reached by this antibiotic in the dental alveolar serum (8), and this could justify the lack of efficacy of CLI in the prevention of BDE.

The cumulative MICs of AMX in the AMX group were higher than that in the control group (MIC\textsubscript{90}, fivefold higher). This could be conditioned by the “selective effect” on some bacterial genera shown by AMX prophylaxis. However, when only Streptococcus spp. were evaluated, the cumulative MIC in the AMX group was also higher than that in the control group (MIC\textsubscript{90}, fourfold higher). This suggests that AMX prophylaxis has another “selective effect” on some bacterial strains based on MICs. No “selective effects” were detected after CLI or MXF prophylaxis.

Despite the local effect of AP, it has been suggested that the total elimination of the bacteria from the gingival sulcus by means of antibiotic administration is impossible (13), probably due to the polymicrobial nature of the gingival flora and the ability of the microorganisms to form biofilms. As a consequence, as in the present series, the AP did not avoid the occurrence of some positive blood cultures in the first 15 min following dental manipulations in the majority of the papers published to date (25, 41). MXF may have a complementary action in later stages, based on the low MICs for the bacteria isolated from the positive postextraction blood cultures, its long half-life, and its ability to reduce the densities of the biofilms formed by the viridans group streptococci isolated from patients with BE and patients with sepsis (33).

In conclusion, in our setting, AMX continues to be the antibiotic of choice for the prevention of BDE in patients who are “at risk” of BE and who are not allergic to PEN. In contrast, we would question the use of prophylaxis with CLI for the prevention of BDE in patients “at risk” of BE with allergy or intolerance to PEN. MXF might represent a safe prophylactic alternative for the prevention of BDE when beta-lactams are contraindicated, although appropriate use is essential if this group of agents is to remain clinically useful.

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