In vitro Activities of Selected New and Long-Acting Cephalosporins against *Pasteurella multocida*

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The activities of six agents commonly used in treating infections of the skin and soft tissues and the action of selected cephalosporins against 15 isolates of *Pasteurella multocida* were assessed by a macro-broth dilution method. Broad-spectrum cephalosporins, including ceftriaxone and cefixime, had excellent in vitro activities (MIC ≤ 0.098) against the isolates tested.

In vitro susceptibility testing has shown that penicillin, ampicillin, and tetracycline have excellent activities against most strains of *Pasteurella multocida* (7, 10). These agents have been used successfully to treat both focal and disseminated infections caused by *P. multocida*. In general, penicillin G has been considered the agent of choice. Poor in vitro activities of penicillinase-resistant penicillins, erythromycin, clindamycin, and aminoglycosides against *P. multocida* (7, 10) and the variable clinical responses in patients treated with these agents (1) make them poor choices for treating patients with such infections.

We assessed the activities of agents routinely used to treat infections of the skin and soft tissues and also tested several new cephalosporins that may be of value in treating focal and disseminated infections caused by *P. multocida*. The excellent in vitro activities of both moxalactam and cefoperazone against *P. multocida* have been described previously (10), and these agents have been recommended for treating patients with infections caused by this organism. The activities of two long-acting cephalosporins, cefixime and cefixime, have not been described. These two agents, because of their long dosing interval, may be useful in treating outpatients with soft tissue and skin infections and may have a role in treating certain patients with suspected, as well as confirmed, *P. multocida* infections.

A total of 15 isolates of *P. multocida* were obtained from subcultures of clinical isolates, incubated overnight on Trypticase soy agar (BBL Microbiology Systems, Cockeysville, Md.) containing 5% sheep blood, harvested, and frozen at −70°C in skim milk broth (Difco Laboratories, Detroit, Mich.). A total of 12 strains of *P. multocida* were isolated from animals and identified at Tufts Veterinary Diagnostic Laboratories, and 3 isolates were obtained from patients who had infected wounds (one dog bite, one cat bite, and one burn) and were hospitalized at Boston City Hospital. Isolates were stored from 1 week to 3 months before testing, and before use they were thawed to room temperature and inoculated into fresh broth.

Each isolate was identified as *P. multocida* by routine laboratory methods, and identification was confirmed by using an API 20E microtine system (Analytab Products, Plainview, N.Y.). Isolates were gram-negative pleomorphic coccobacilli that produced no hemolysis when incubated on sheep blood agar. All isolates were oxidase positive (as determined by Kovacs reagent spot test), indole positive, and nonmotile. Of all the isolates, 88% produced acid in sucrose, 6% fermented sorbitol, and 25% fermented manitol.

Solutions of antimicrobial agents were prepared in fresh, modified (thymidine poor) Mueller-Hinton broth (Difco) at concentrations of 200 μg/ml. The modification of the broth permits in vitro antimicrobial activity testing of agents that include combinations of sulfamethoxazole and trimethoprim (5). Solutions were serially diluted in broth in polystyrene tubes (12 by 75 mm; Fisher Scientific Co., Pittsburgh, Pa.) to yield final concentrations of between 50 and 0.012 μg/ml.

Organisms were incubated overnight (16 to 18 h) in broth. The overnight growth of each isolate was estimated to be 10⁶ organisms per ml by nephelometry. Each isolate was then diluted in fresh broth to an approximate concentration of 10⁵ to 10⁶ organisms per ml. A 0.5-ml amount of this dilution was pipetted into each tube to achieve a final tube volume of 1 ml. The size of the inoculum was confirmed by both serial dilutions and the pour plate technique and ranged from 1.8 × 10⁶ to 1.2 × 10⁷ CFU/ml.

After inoculation, tubes were vortexed for 10 s and incubated overnight (16 to 18 h) at 37°C. The concentration of antimicrobial agent resulting in no visible cloudiness after overnight incubation was defined as the MIC. Bacterial growth was assessed by plating a 10-μl sample of broth onto sheep blood agar. Plates were incubated for 24 h at 37°C, and the MBC was taken as the concentration of antimicrobial agent resulting in a >99.9% reduction in organisms per milliliter of the initial inoculum, provided that this inoculum exceeded 5.0 × 10⁷ CFU/ml.

The MIC (of 15 isolates) and the MBC (of 13 isolates) of 11 antimicrobial agents for *P. multocida* were calculated (Table 1). Cefoperazone, moxalactam, ceftriaxone, and cefixime showed the greatest activities. A greater-than-two-fold dilution disparity between the MIC and the MBC was not found for any of the isolates tested.

A variety of antimicrobial agents have been used in treating infections caused by *P. multocida*. The MICs and MBCs of penicillin G, penicillin V, erythromycin, oxacillin, and cephalothin for the isolates we studied are similar to those previously reported for 17 human isolates (7). These results further indicate the use of penicillin in treating infections caused by *P. multocida* and confirm the poor in vitro activities of erythromycin and oxacillin against this pathogen.

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Our data and a previous report (10) together suggest that isolates of *P. multocida* obtained from both animals and humans are susceptible in vitro to several broad-spectrum cephalosporins. The excellent in vitro activities of cefoperazone, moxalactam, ceftriaxone, and cefixime against *P. multocida* suggest that these agents will be useful in treating infections caused by this organism. Because of their pharmacokinetic properties, such as excellent penetration into the central nervous system and long serum half-life, some of these new agents may be preferable to penicillin, ampicillin, or tetracycline in treating certain infections. In addition, the broader spectrum of antibacterial activity of these newer agents may make their use preferable to conventional therapy in treating polymicrobial wound infections. However, before recommendations can be made for the use of these agents instead of or as alternatives to penicillin, ampicillin, or tetracycline, both further in vitro testing of isolates obtained from patients and clinical experience in treating focal and disseminated infections are necessary.

We thank Andrew Onderdonk and William O'Brien for providing the isolates obtained from animals.

**LITERATURE CITED**


**TABLE 1. Susceptibility of *P. multocida* to selected antimicrobial agents**

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC (µg/ml)</th>
<th>MBC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Median</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>0.098–1.56</td>
<td>0.39</td>
</tr>
<tr>
<td>Cefixime</td>
<td>&lt;0.012–0.098</td>
<td>0.024</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>&lt;0.012–0.024</td>
<td>&lt;0.012</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>&lt;0.012–0.19</td>
<td>0.024</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>0.098–0.39</td>
<td>0.19</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>0.78–12.5</td>
<td>3.12</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>&lt;0.012–0.312</td>
<td>1.56</td>
</tr>
<tr>
<td>Moxalactam</td>
<td>&lt;0.012–0.049</td>
<td>0.024</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>0.19–3.12</td>
<td>1.56</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>0.049–0.39</td>
<td>0.098</td>
</tr>
<tr>
<td>Penicillin V</td>
<td>0.098–0.39</td>
<td>0.19</td>
</tr>
</tbody>
</table>

For MIC calculations, $n = 15$, and for MBC calculations, $n = 13$. 

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