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Synergistic effect of cefixime and cloxacillin combination against common bacterial pathogens causing community acquired pneumonia

The most common etiologic agent in virtually all studies of community acquired pneumonia (CAP) is Streptococcus pneumoniae, which accounts for approximately two-third of the cases of bacteremic pneumonia.[1] Other pathogens include Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Staphylococcus aureus, Streptococcus pyogenes and Klebsiella pneumoniae and other gram-negative rods. A number of antimicrobial agents have been established for the management of CAP. No single agent is efficacious against all pathogens. A number of authors have reported that a synergistic antibacterial effect may result when either two penicillins or a penicillin and a cephalosporin are used in combination against certain gram-negative bacilli. The mechanism for this synergistic effect was shown to be a competitive inhibition of β-lactamase by one of the penicillins, which protects the second penicillin from inactivation by hydrolysis. Here we studied the synergistic effect of cloxacillin and cefixime against the common bacterial pathogens causing CAP.

Antimicrobial-sensitive standard strains of Escherichia coli ATCC 35218, Pseudomonas aeruginosa ATCC 27853, Klebsiella pneumoniae ATCC 47152, Streptococcus pneumoniae ATCC 49618, Haemophilus influenzae ATCC 49247 and Staphylococcus aureus ATCC 29213 were tested in this study. The MIC of cloxacillin and cefixime was determined by the agar dilution method, according to clinical laboratory standards institute (CLSI, 2005).[2]

Combinations of cloxacillin and cefixime were tested against each microorganism by the checkerboard method, with the MICs ranging from 1/32 µg/ml to 4 µg/ml. Fractional inhibitory concentration (FIC) was calculated for each antibiotic for every organism. The following formulas were used:

FIC index = FIC of drug A + FIC of drug B.
FIC of drug A = MIC of drug A in combination/MIC of drug A alone.
FIC of drug B = MIC of drug B in combination/MIC of drug B alone.

Synergy was defined as an FIC index of ≤0.5. Indifference was defined as an FIC index of ≥0.5 but of ≤4.0. Antagonism was defined as an FIC index of >4.0.

The MIC and FIC indices of both the drugs against all the strains are shown in Table 1. Clear synergism is seen against S. pneumoniae and H. influenzae. Although no definite synergism or antagonism could be demonstrated against the rest of the organisms, a beneficial effect is definitely seen.

A combination of chloramphenicol and ampicillin had shown synergism against H. influenzae.[3] Salverezza et al., studied patients of uncomplicated CAP and found that 28 of the 30 given cefixime were cured. One patient in the cefixime group had a partial response and one patient who had P. aeruginosa infection failed treatment.[4] Many enterobacteriace isolates exhibit a high frequency of resistance to the earlier generation cephalosporins, such as cephalothin, cefazolin and cefoxitin, with MICs > 64 µg/ml.[5]

We demonstrated the synergistic effect of cloxacillin and cefixime used in combination against S. pneumoniae and H. influenzae, the commonest causes of CAP. The strains used in present experiment were standard strains. There is the need to test this combination in clinical isolates; especially worth noting will be the response in drug-resistant isolates. If the combination proves effective against β-lactamase producing H. influenzae and penicillin-resistant pneumoniae, the clinical trials would be worthwhile.

### Table 1
Summary of synergy test results

<table>
<thead>
<tr>
<th>Strains</th>
<th>MIC when single drug was used</th>
<th>MIC when combination was used</th>
<th>FIC index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cloxacillin</td>
<td>Cefixime</td>
<td>Cloxacillin</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>2 µg/ml</td>
<td>1 µg/ml</td>
<td>0.0625 µg/ml</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>1 µg/ml</td>
<td>0.25 µg/ml</td>
<td>0.25 µg/ml</td>
</tr>
<tr>
<td>S. aureus</td>
<td>1 µg/ml</td>
<td>32 µg/ml</td>
<td>0.5 µg/ml</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>256 µg/ml</td>
<td>32 µg/ml</td>
<td>256 µg/ml</td>
</tr>
<tr>
<td>E. coli</td>
<td>128 µg/ml</td>
<td>0.5 µg/ml</td>
<td>4 µg/ml</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>256 µg/ml</td>
<td>0.5 µg/ml</td>
<td>128 µg/ml</td>
</tr>
</tbody>
</table>
Agarwal et al.: Synergistic effect of cefixime and cloxacillin


