Intracellular MRSA, VISA and VRSA Are Sensitive to Cloxacillin and Meropenem

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Abstract

Objectives: Exposure of methicillin-resistant S. aureus (MRSA) to acid pH restores their susceptibility to β-lactams (Sabath et al., AAC, 1972). In phagocytes, intracellular forms of S. aureus are largely restricted to the phagolysosomes, where pH is acidic (about 5.5). We have, therefore, examined the intraphagocytic activity of cloxacillin (CLX) and meropenem (MEM) against selected methicillin-sensitive S. aureus (MSSA), methicillin-resistant S. aureus (MRSA), VISA and VRSA strains.

Methods: MICs were determined by micro-dilution method using pH-adjusted Mueller Hinton Broth with NaCl 2%. Intracellular activity was assessed in human THP-1 macrophages exposed to extracellular concentrations equivalent to human Cmic (total drug, MEM 50 μg/mL, CLX 8 μg/mL) and expressed as a difference in cell-associated CFU after 24h (DCFU) between controls (no antibiotics, approx. 2 log CFU) and tests.

Results: The table shows the MICs in neutral and acid broth and the intracellular activity for the 4 strains studied.

<table>
<thead>
<tr>
<th>Strains</th>
<th>CLX</th>
<th>MEM</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>pH 7.4</td>
<td>pH 7.4</td>
</tr>
<tr>
<td>MSSA ATCC 29213</td>
<td>0.125</td>
<td>0.06</td>
</tr>
<tr>
<td>MRSA ATCC 33591</td>
<td>16</td>
<td>0.06</td>
</tr>
<tr>
<td>MSSA NRS18</td>
<td>3</td>
<td>0.06</td>
</tr>
<tr>
<td>VRSA VRS2</td>
<td>32</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Conclusions: The similar intracellular activities of CLX and MEM against MRSA, VISA and VRSA in comparison with MSSA, in spite of their marked differences in susceptibility when tested at pH 7.4 in broth, may result from restoration of susceptibility due to acid pH in the phagolysosomal environment. Conventional MIC determinations are inadequate to accurately predict the susceptibility of the intracellular forms of resistant S. aureus.

Background

MRSA show a high level of resistance to β-lactams, in relation with the expression of a modified PBP (PBP2a). However, the activity of β-lactams against MRSA is restored in acidic conditions.1 This may be of interest for staphylococcal infections developing in acidic environments. In particular, S. aureus has the potential of surviving within the phagosomal compartments of phagocytic cells (where pH is acidic). In macrophages, we recently showed that meropenem does exert intracellular activity against MSSA.2

Results

1 Susceptibility testing

In broth, acid pH restores the activity of CLX and MEM towards MRSA, including VISA and VRSA.

2 Intracellular activity

• CLX and MEM display a similar concentration-dependent activity against S. aureus
• Static concentrations and Emax (maximal effect) are similar whatever the resistance phenotype of the strain

Change in cfu (log10) per mg of cell protein observed after 24 h of incubation of infected THP-1 macrophages exposed to extracellular concentrations of drugs ranging from 0.01 to 1,000-fold their MIC determined at pH 5.5. All values are mean ± SEM (n=3).

References


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