Pharmacological comparison of the activity of antibiotics against intracellular S. aureus

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**S. aureus** is an opportunistic intracellular pathogen

infection of the vacuolar apparatus in macrophages

Seral et al. (2003) AAC 47:2283-92
PK-PD to rationalize antibiotic choice

- Metabolism
- Binding
- Cooperation with host defences
- Physico-chemical conditions
- Bacterial responsiveness
- Accumulation and bioavailability
- Influx
- Efflux

Aim of the study

to compare the concentration-effect relationships
• against extracellular AND intracellular *S. aureus*
• for antibiotics with markedly different cellular pharmacokinetic properties
Methods

**Extracellular activity**
- exposure of bacteria to antibiotics (0.05-1000 X MIC) in RPMI medium

**Intracellular activity**
- infection of THP-1 human macrophages (4 bacteria/cells)
- elimination of extracellular bacteria by washing with GEN
- incubation for 24 h with antibiotics (0.05-1000 X MIC) or to GEN 1 X MIC (control)

Based on Seral et al. (2003) AAC 47:2283-92
Extracellular activity

All AB are concentration-dependent
Intracellular activity

Decrease of CFU is observed at clinically-achievable concentr.
Extracellular activity vs intracellular activity

But intracellular activity is always < than extracellular activity
Comparison of concentrations needed for a static effect

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Extracellular</th>
<th>Intracellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>OXA</td>
<td>0.52</td>
<td>2.09</td>
</tr>
<tr>
<td>MXF</td>
<td>0.29</td>
<td>0.63</td>
</tr>
<tr>
<td>GEN</td>
<td>0.30</td>
<td>2.09</td>
</tr>
<tr>
<td>ORI</td>
<td>0.29</td>
<td>4.79</td>
</tr>
</tbody>
</table>

- OXA: X 3-4
- MXF: X 6-12
Comparison of maximal effects

<table>
<thead>
<tr>
<th>antibiotic</th>
<th>maximal effect (log CFU decrease from 0h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>extracellular</td>
</tr>
<tr>
<td>OXA</td>
<td>-3.70</td>
</tr>
<tr>
<td>MXF</td>
<td>-4.29</td>
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<tr>
<td>GEN</td>
<td>-5.76</td>
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<tr>
<td>ORI</td>
<td>-5.55</td>
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<tr>
<td>antibiotic</td>
<td>effect at Cmax</td>
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<td></td>
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</tr>
<tr>
<td>OXA</td>
<td>-2.12</td>
</tr>
<tr>
<td>MXF</td>
<td>-2.64</td>
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<tr>
<td>GEN</td>
<td>-0.66</td>
</tr>
<tr>
<td>ORI</td>
<td>-2.88</td>
</tr>
</tbody>
</table>
Conclusion

Intracellular activity is always << extracellular activity
• irrespective to the antibiotic accumulation level
• for all drug classes tested

Acid pH is not the only culprit for this decrease of activity

► higher extracellular concentrations are needed to kill intracellular bacteria
► intracellular activity cannot been predicted from accumulation levels only, and should therefore be tested in appropriate models
► among the drugs studied, a definite bactericidal intracellular effect at clinically achievable extracellular concentrations can be obtained for a few of them only (ORI, MXF) ...