Clinical relevance of bacterial persistence and tolerance

Alex Soriano
Hospital Clínic of Barcelona
CASE 1  
persistent bacteremia due to *S. aureus*

CASE 2  
psoas abscess with persistent fever

CASE 3  
knee prosthetic joint infection

CASE 4  
recurrent episodes of osteomyelitis
CASE 1

Male of 27 y-o admitted to ICU because of fever and severe sepsis and BC + MSSA.

**Cloxacillin 2g/4h i.v.**
- d1 BC+ MSSA
- Cloxacillin MIC= 0.5 mg/L

**Cloxacillin + Daptomycin 700 mg/24h i.v.**
- d7 BC+ MSSA
- d10 BC+ MSSA
- Cloxacillin MIC= 0.5 mg/L

Ecocardiography was negative.

Cloxacillin \(C_{\text{max}}> 100\) mg/L

Daptomycin \(C_{\text{max}}> 60\) mg/L

- 48 patients with S. aureus CRB were studied with an ecography.
- In 71% of cases a thrombosis was observed in the vein were the catheter was placed.

PB ≥ 3 days after removing the catheter and adequate antibiotic treatment (n=203)

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514 episodes of SAB were prospectively registered from 2006 to 2011 in Hospital Clínic. PSAB was detected in 23% of cases.

**RESULTS:**

PSAB was an independent predictor of 30d-mortality (OR: 2.5, CI95%: 1.3-4.6, \( P = 0.003 \))

Risk factors for PSAB:

- Endocarditis
- Abdominal abscess
- Arthritis

“environment”

“genetic bg”

**environment rich in cationic peptides**

“stringent ambient”

30 h post- daptomycin exposure

- selection of tolerant strains
Fowler V, et al. Persistent Bacteremia Due to MRSA Infection Is Associated with agr Dysfunction and Low-Level In Vitro Resistance to Thrombin-Induced Platelet Microbicidal Protein. J Infect Dis 2004; 190:1140-9

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Resolving bacteremia</th>
<th>Persistent bacteremia</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 18)</td>
<td>(n = 21)</td>
<td></td>
</tr>
<tr>
<td>PFGE genotype A</td>
<td>8 (44.4)</td>
<td>18 (85.7)</td>
<td>.02</td>
</tr>
<tr>
<td>agr AIP genotype II</td>
<td>4 (22.2)</td>
<td>0</td>
<td>.04</td>
</tr>
<tr>
<td>Survival after exposure to tPMP</td>
<td>11.6 ± 6.5</td>
<td>22.4 ± 14.8</td>
<td>.005</td>
</tr>
<tr>
<td>Defective δ-lysin production</td>
<td>7 (38.9)</td>
<td>15 (71.4)</td>
<td>.057</td>
</tr>
<tr>
<td>Defective Triton lysis</td>
<td>8 (44.4)</td>
<td>5 (23.8)</td>
<td>.20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multiple logistic regression</th>
<th>OR (95% CI)</th>
<th>P</th>
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BP (≥7 d): 18 strains

NP (<7 d): 18 strains

<table>
<thead>
<tr>
<th>hNP-1 (% survival)</th>
<th>3.51 (1.05–11.8)</th>
<th>0.042</th>
</tr>
</thead>
<tbody>
<tr>
<td>tPMPs (% survival)</td>
<td>1.09 (1.02–1.16)</td>
<td>0.004</td>
</tr>
<tr>
<td>Fibronectin binding ($A_{57}$)</td>
<td></td>
<td></td>
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<tr>
<td>Endothelial cell binding (% binding)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biofilm formation ($A_{490}$)</td>
<td>17.04 (1.11–262)</td>
<td>0.042</td>
</tr>
</tbody>
</table>
Male of 72 y-o transferred from other hospital with a psoas abscess and persistent fever after 16 days on cloxacillin 2g/4h + levofloxacin 500 mg/12h iv.

CASE 2

2 mL of pus were obtained for culture but it was not possible to leave a drain tube. Culture was positive for MSSA susceptible to cloxa and levo. Rifampin 600 mg/12h iv was added and the patient became afebrile.
CASE 3

Female of 66 y-o with a TKA was submitted to our outpatient clinic because 5 months of pain and redness over the prosthetic knee. Synovial fluid culture was positive for MSSA. She refused any intervention and after 12 days on systemic antibiotics the SF remained positive.

cloxacillin 2 g/4h i.v. + linezolid 600 mg/12h p.o.

d1
synovial fluid
- glucose: 6 mg/dL
- proteins: 56 mg/dL
- leucocytes: 38.000 cel/mm³
- %PMN: 96
- culture: MSSA (rifamp-R)

d12
synovial fluid
- glucose: 25 mg/dL
- proteins: 48 mg/dL
- leucocytes: 5400 cel/mm³
- %PMN: 98
- culture: MSSA
biofilm

exponential phase

stationary phase

<table>
<thead>
<tr>
<th>Months from surgery</th>
<th>cured/treated</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>20 / 24</td>
<td>84</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>19 / 36</td>
<td>53</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>4 / 13</td>
<td>30</td>
</tr>
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Mean duration of antibiotics: *6 months*
daily intra-articular administration of high concentration of daptomycin: 350 mg dissolved in 250 mL of saline (>1000 mg/L)

1ª positive culture (20-9-2013)

2ª positive culture

3ª positive culture

4ª positive culture

5ª positive culture

6ª negative culture

7ª negative culture

8ª negative culture

Linezolid was administered for 4 weeks and she is maintained with suppressive therapy with minocycline (last control 4-4-2014, asymptomatic)
Male of 57 y-o with recurrent episodes of pain and purulent drainage through a cutaneous fistulae in the left thigh. MSSA was isolated from fistulae.

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Intracellular activity against MSSA (SCV) at $C_{\text{max}}$
### Intracellular Activity of Antibiotics in a Model of Human THP-1 Macrophages Infected by a S. aureus SCV Isolated from a Cystic Fibrosis Patient.


<table>
<thead>
<tr>
<th>Drug</th>
<th>Extracellular concn (mg/liter)</th>
<th>Intracellular activity indicated time</th>
<th>Drug alone</th>
<th>24 h</th>
<th>72 h</th>
<th>Drug with oritavancin</th>
<th>24 h</th>
<th>72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>18</td>
<td>-1.40 ± 0.18</td>
<td>-3.39 ± 0.21</td>
<td>-3.19 ± 0.10</td>
<td>-4.50</td>
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<tr>
<td>Vancomycin</td>
<td>50</td>
<td>-0.11 ± 0.04</td>
<td>-1.35 ± 0.08</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oxacillin</td>
<td>64</td>
<td>-0.06 ± 0.04</td>
<td>-1.31 ± 0.06</td>
<td>-2.61 ± 0.11</td>
<td>-3.25 ± 0.06</td>
<td></td>
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</tr>
<tr>
<td>Fusidic acid</td>
<td>30</td>
<td>-0.33 ± 0.07</td>
<td>-0.87 ± 0.04</td>
<td>ND</td>
<td>ND</td>
<td></td>
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<tr>
<td>Gentamicin</td>
<td>18</td>
<td>-0.44 ± 0.09</td>
<td>-1.54 ± 0.09</td>
<td>-2.90 ± 0.09</td>
<td>-3.70 ± 0.13</td>
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<tr>
<td>Clindamycin</td>
<td>4</td>
<td>-0.27 ± 0.10</td>
<td>-1.30 ± 0.08</td>
<td>-2.63 ± 0.12</td>
<td>-3.54 ± 0.11</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>4</td>
<td>-1.20 ± 0.05</td>
<td>-2.53 ± 0.04</td>
<td>-3.26 ± 0.13</td>
<td>-4.18 ± 0.16</td>
<td></td>
<td></td>
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<tr>
<td>Linezolid</td>
<td>16</td>
<td>-0.39 ± 0.01</td>
<td>-1.52 ± 0.08</td>
<td>-2.73 ± 0.09</td>
<td>-3.60 ± 0.06</td>
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</tr>
<tr>
<td>Quinupristin-dalfopent</td>
<td>11</td>
<td>-0.22 ± 0.03</td>
<td>-2.06 ± 0.16</td>
<td>-2.82 ± 0.15</td>
<td>-4.18 ± 0.32</td>
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</tr>
<tr>
<td>Daptomycin</td>
<td>57</td>
<td>-0.39 ± 0.02</td>
<td>-1.38 ± 0.01</td>
<td>-2.59 ± 0.05</td>
<td>-2.97 ± 0.16</td>
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<tr>
<td>Oritavancin</td>
<td>25</td>
<td>-2.53 ± 0.10</td>
<td>-2.98 ± 0.11</td>
<td>NA</td>
<td>NA</td>
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</tbody>
</table>

### Intracellular activity against MSSA (SCV) at C<sub>max</sub>
high inoculum infection: rapidly growing bacteria/persistent bacteria (genetic background)

environment (thrombo, abscess, biofilm, intracellular space)

innate immunity & antimicrobial “pressure”

“persisters”

antibiotic combinations

high local [antibiotic]

surgical debridement

failure - mortality