Combination therapy in complicated infections due to S. aureus

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IDIBAPS
Sureward, et al.

Identification and treatment of the Staphylococcus aureus reservoir in vivo.


Staphylococcal dissemination to different organs 30 min after i.v. Infection (using a real-time imaging)

Liver, Kupfer cell (purple)  
S. aureus (green)

Large cluster of S. aureus inside of KC. Located in phagolysosomes.

eradication from blood

Liver

Kidney

Graph showing the number of cfu/organ over time (h) with liver and kidney data points.

- Vancosomes: vancomycin within liposomes
- vancomycin (1h before or after)
Animal model of *S. aureus* bacteremia. Treatment started after 24h of the infection.
Case #1
Medical history: A 27 y-o man, without co-morbidity. January 2015 was admitted to our hospital. A week before admission suffer an accidental puncture in the foot. After that, starts with arthromialgia, chest and lumbar pain and fever.

Physical examination: bad general status, BP 128/77 mmHg, HR140 x’, BR 40x’, SpO₂ 93% (basal). Crackles in the lower right lung and no other alterations (the food was normal).

Blood test: pH 7.39; pCO₂ 33.9 mmHg; pO₂ 58 mmHg; Bicarbonato 20.1 mmol/L; CRP 30.7 mg/dL; Creatinin 1.19 mg/dL; Lactate 39.7 mg/dL; WBC 1600/mm³; Hemoglobin 15.4 mg/dL; Platelets 95.000; PT 60.6%; APTT 33.6 seg; Fibrinogen 4.6 g/L; FDP positive; RNI 1.3
The patient’s condition progressively worsens and needed ICU admission and vaso-active and ventilatory support.

4/4 blood cultures + MSSA (TTP: <10h)
Which is your first diagnosis?

1. CAP associated with Influenza virus
2. Right-sided endocarditis with pulmonary embolisms
3. Deep venous thrombosis related with the previous food puncture
4. Other diagnosis
Characteristics of patients admitted to ICU during H1N1 epidemics (n=683) in EEUU:

<table>
<thead>
<tr>
<th>microorganism</th>
<th>confirmed N=154*</th>
<th>bacteremia</th>
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</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>47 (30%)</td>
<td>23 (49%)</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>17 (11%)</td>
<td>10 (59%)</td>
</tr>
<tr>
<td>grup A streptococci</td>
<td>4 (3%)</td>
<td>-</td>
</tr>
</tbody>
</table>

* bacterial co-infection was suspected in 207 cases (30%)
The patient’s condition progressively worsens and needed ICU admission and vasoactive and ventilatory support.

4/4 blood cultures + MSSA (TG: <10h)

monotherapy with a β-lactam (cloxacinilin)

cloxacinilin 12g CI + clindamycin 600 mg/6h
Stevens DL, et al
Clin Infect Dis 2006

antibacterial activity

toxin production
After 7 days patient was still febrile and blood cultures remained positive. A CT scan ...

Echocardiography (TT and TE) was negative
Are you going to add a third antibiotic

cloxacillin + clindamycin + daptomycin
after 6 weeks of antibiotic treatment + heparin, the CT scan revealed the disappearance of cava thrombus
S. aureus → local infection

- tissue inflammation
- tissue necrosis
- purulence formation
- hematogenous spread
- septic metastasis

β-lactams
- glycopeptides
- daptomycin
- fosfomycin
- cotrimoxazol
- aminoglycosides
S. aureus → local infection

- tissue inflammation
- tissue necrosis
- purulence formation
- hematogenous spread
- septic metastasis

β-lactams x 2
- glycopeptides
- daptomycin
- fosfomycin
- cotrimoxazol
- aminoglycosides

Authors present a clinical case of MSSA persistent bacteremia that was cleared 24h after starting ERT+CZ.

Synergism was confirm in 34/35 clinical strains (DD)

1. target different PBP (ERT-PBP1 + CZ-PBP2)
2. overcome the reduced activity of CZ against SA producing type A b-lactamase (even in high-inoculum)
3. potentiates the activity of cationic peptides
**S. aureus**

- Local infection
  - Tissue inflammation
  - Tissue necrosis
  - Purulence formation
  - Hematogenous spread
  - Septic metastasis

**β-lactams**
- Daptomycin
- Fosfomycin
- Cotrimoxazol
- Aminoglycosides

**Glycopeptides**

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Days of bacteremia
- MICv <1.5 mg/L
  3 (3.35) 0.06 1.94 (1.79)
- MICv ≥1.5 mg/L
  3 (1.5-6.5) 0.22 1.5 (1-2)
Mortality 30-d (%)
  5 (17) 0.91 5 (16)
>50% increase Cr (%)
  3 (11) 0.22 8 (28)

HR 0.74 (95% CI 0.49, 1.26); log rank p=0.14

Number at risk
Standard 29 12 8 6 4 2 2 1
Combination 31 11 4 2 1 0 0 0
S. aureus → local infection

- tissue inflammation
- tissue necrosis
- purulence formation
- hematogenous spread
- septic metastasis

- ß-lactams
- glycopeptides
- daptomycin
- fosfomycin
- cotrimoxazol
- aminoglycosides

Authors present 3 endocarditis (1 MSSA with a PV-IE) successfully treated with daptomycin + fosfomycin without surgery

Synergism was confirmed in 7/7 strains (KC)
**S. aureus**

- Local infection
  - Tissue inflammation
  - Tissue necrosis
  - Purulence formation
  - Hematogenous spread
  - Septic metastasis

**β-lactams**
- Glycopeptides
- Daptomycin
- Fosfomycin
- Cotrimoxazol
- Aminoglycosides
• Endocarditis (n=12), vascular graft infection (n=2), complicated bacteremia (n=2).
• Therapy had previously failed to other options.
• Blood cultures were negative 72 hours after the first dose.
• Success rate was 69%
• There were no episodes of breakthrough bacteremia or relapse.
• A patient with liver cirrhosis died of multiorgan failure secondary to sodium overload.
S. aureus

Local infection

- Tissue inflammation
- Tissue necrosis
- Purulence formation
- Hematogenous spread
- Septic metastasis

- β-lactams
- Glycopeptides
- Daptomycin
- Fosfomycin
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**Fowler V, et al.** Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus.*


<table>
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<tr>
<th>Antibiotic</th>
<th>Microbiological Failure (Persistent Bacteremia/Relapse)</th>
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<tr>
<td>Daptomycin</td>
<td>19/120 (15.8%)</td>
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<tr>
<td>Vancomycin</td>
<td>9/53 (16.9%)</td>
</tr>
<tr>
<td>Anti-staphylococcal ß-L</td>
<td>2/62 (3.2%)</td>
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</table>

**Graph**

- Control
- t-PMP alone
- oxa (=MIC)
- t-PMP + oxa (=MIC)

β-lactams have a **dual effect** a direct bactericidal activity and increase the bactericidal activity of innate immunity

*S. aureus* MIC = 4 mg/L
membrane
Resistance to cationic peptides and daptomycin is associated with an increase in the net positive charge of the external surface of the membrane.
β-lactams reduce the positive charge and increases the daptomycin binding to the membrane.

*J Infect Dis* 2017; 215: 80-7

- Virulence attenuation
- Increase susceptibility to PMN
Dhand, et al. Use of Antistaphylococcal ß-Lactams to Increase Daptomycin Activity in Eradicating Persistent Bacteremia Due to MRSA: Role of Enhanced Daptomycin Binding

Clin Infect Dis 2011; 53:158-163

Synergism was not observed with all the strains.


daptomycin S (0.5 mg/L) h-VISA Simulation: DAP 10 mg/kg, CFT 600 mg/8h, VAN 2 g/12h
Daptomycin plus ceftaroline was used in 26 cases of SAB (MRSA 20, MSSA 2, VISA 2, and MRSE 2).

Indication: 31% second-line therapy (8 cases), 50% third-line therapy (13 cases), and 19% fourth-line therapy (5 cases).

Prior DAP+CTL patients were bacteremic for a median of 10 days (range, 3–23 days), and the bacteremia cleared in a median of 2 days (range, 1–6 days) after daptomycin plus ceftaroline was started (not related with surgical procedure).