Rapid diagnosis and prolonged antimicrobial therapy for the elimination of biofilm infections

Alex Soriano
Hospital Clínic of Barcelona
University of Barcelona
IDIBAPS
When “rapid” diagnosis of infection is necessary for orthopedic surgeon?

- is this patient infected?
- partial revision or total revision?
- after surgery, we have to maintain antibiotic treatment/prophylaxis until definitive culture results (5-7 days)?
- no reliable serum biomarkers
- pre-operative aspiration culture S and Sp is 60-70%

chronic pain (>3 months)
CRP 1.4 mg/dL
aspiration -
frozen section (15-30’):
-pathologist on call
-expert on this analysis

> 5 PMN / field (x400) in > 5 fields


Cut-off point: 5200 ng/mL

1 FN

5 FP

<table>
<thead>
<tr>
<th>Author, year</th>
<th>SENSITIVITY (95% CI)</th>
<th>SPECIFICITY (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha-defensin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deirmengian, 2015 (31)</td>
<td>1.00 [0.98 - 1.00]</td>
<td>0.85 [0.83 - 0.87]</td>
</tr>
<tr>
<td>Frangiamore, 2015 (28)</td>
<td>0.64 [0.31 - 0.89]</td>
<td>0.95 [0.77 - 1.00]</td>
</tr>
<tr>
<td>Deirmengian, 2014 (13)</td>
<td>0.97 [0.86 - 1.00]</td>
<td>0.96 [0.90 - 0.99]</td>
</tr>
<tr>
<td>Deirmengian, 2014 (27)</td>
<td>1.00 [0.88 - 1.00]</td>
<td>1.00 [0.95 - 1.00]</td>
</tr>
<tr>
<td>Deirmengian, 2015 (17)</td>
<td>1.00 [0.85 - 1.00]</td>
<td>1.00 [0.85 - 1.00]</td>
</tr>
<tr>
<td>Bingham, 2014 (26)</td>
<td>1.00 [0.82 - 1.00]</td>
<td>0.95 [0.84 - 0.99]</td>
</tr>
<tr>
<td><strong>COMBINED</strong></td>
<td>1.00 [0.82 - 1.00]</td>
<td>0.96 [0.89 - 0.99]</td>
</tr>
</tbody>
</table>

$Q = 281.02$, df = 5.00, $p < 0.001$

$I^2 = 98.22 [97.54 - 98.90]$

$Q = 404.70$, df = 5.00, $p < 0.001$

$I^2 = 98.76 [98.35 - 99.18]$
Deirmengian C, et al. The Alpha-defensin Test for Periprosthetic Joint Infection Responds to a Wide Spectrum of Organisms


ELISA test and requires 3-4h

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Synovasure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>67% (95% CI 35%-89%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>93% (95% CI 75%-99%)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>80% (95% CI 44%-96%)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>87% (95% CI 68%-96%)</td>
</tr>
<tr>
<td>Likelihood ratio—positive</td>
<td>9.33 (95% CI 2.32-37.63)</td>
</tr>
<tr>
<td>Likelihood ratio—negative</td>
<td>0.36 (95% CI 0.16-0.80)</td>
</tr>
<tr>
<td>Overall accuracy</td>
<td>85% (95% CI 70%-93%)</td>
</tr>
<tr>
<td>AUC</td>
<td>0.80 (95% CI 0.62-0.97)</td>
</tr>
</tbody>
</table>
Bosch J, et al. usefulness of synovial fluid in blood culture flasks and periprosthetic samples for the microbiology diagnosis of prosthetic joint infections. *Not published*

<table>
<thead>
<tr>
<th>Sample</th>
<th>Nº samples</th>
<th>% positive</th>
<th>% positive in ≤24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF (BC flask)</td>
<td>231</td>
<td>83.5</td>
<td>S. aureus 82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CoNS 49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GNB 78</td>
</tr>
<tr>
<td>Solid sample</td>
<td>232</td>
<td>60.8</td>
<td></td>
</tr>
</tbody>
</table>

Samples from 120 patients with PJI (≥2 positive intraoperative samples)
Minassian, et al. Use of an automated blood culture system (BD BACTEC™) for diagnosis of prosthetic joint infections: easy and fast

*BMC Infectious Diseases* 2014, 14:233

**Solid sample**

Vortex 15” 40 Hz in 3 mL of saline with glass beads

0.5 mL → 0.5 mL
Minassian, et al. Use of an automated blood culture system (BD BACTEC™) for diagnosis of prosthetic joint infections: easy and fast

*BMC Infectious Diseases 2014, 14:233*

- **AERobic N = 350**
  - 70% 100%

- **ANAerobic N = 360**
  - 70% 100%

N = 79 PJIs, 66 (83.5%) positive cultures, 13 (16.5%) negative cultures
Rapid diagnosis and **prolonged antimicrobial therapy** for the elimination of biofilm infections

Alex Soriano
Hospital Clínic of Barcelona
University of Barcelona
IDIBAPS
Bacteremia +SIRS


- % of internal surface covered by biofilm
- Probability of developing bacteremia
- "extension" "maturity"
“planktonic” bacteria

Planktonic cells

“early” biofilm

Biofilm cells
early biofilm

late biofilm

planktonic bacteria

acute infections

chronic infections

ESCMID eLibrary © by author
“planktonic” bacteria

Planktonic cells

“early” biofilm

Biofilm cells

“late” biofilm

Biofilm cells
“planktonic” bacteria

bactericidal antibiotic (5-10 d)

“early” biofilm

anti-biofilm antibiotic (2-6 m)

“late” biofilm

<table>
<thead>
<tr>
<th>Symptoms duration</th>
<th>cured/treated</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 month</td>
<td>20 / 24</td>
<td>84</td>
</tr>
<tr>
<td>&gt; 1 month</td>
<td>19 / 36</td>
<td>53</td>
</tr>
<tr>
<td>&gt; 6 month</td>
<td>4 / 13</td>
<td>30</td>
</tr>
</tbody>
</table>

Mean treatment duration: 6 months

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Short (n=48)</th>
<th>Long (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success rate (%)</td>
<td>87.5</td>
<td>89.5</td>
</tr>
</tbody>
</table>

In April 2006 we shortened the total antibiotic treatment duration in total knee arthroplasty (TKA) PJIs from 6 months to 3 months and in total hip arthroplasty (THA) PJIs from 3 months to 2 months.


Patients: haematogenous or early post-surgical PJI caused by staphylococci with a stable implant and managed with DAIR

Levofloxacin (750 mg/24h) + rifampin (600 mg/24h)

- 8 weeks N=24
- 3 m for hips N=20
- 6 m for knees N=20
Open questions

1. In case of fluoroquinolone resistance, which is the alternative antibiotic? and the length of antibiotic therapy should be the same?

2. When rifampin cannot be used, is it possible to treat foreign-body infections without removing the implant?

3. Are these results valid for infections caused by other microorganisms (Enterococcus spp., streptococci, GNB or polymicrobial)?
“planktonic” bacteria

“early” biofilm

“late” biofilm

bactericidal antibiotic (5-10 d)

anti-biofilm antibiotic (2-6 m)

Implant removal or “suppresive” antibiotic