How to reach consolidation in an infected bone, microbiological and antibiotic principles

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Source of the infection

• Open fracture: through the skin
• During surgery: contamination of the fracture site during the intervention
• Spread of a wound infection to the fracture site
• Spread of a deep infection foci (abcess) to the fracture site

• Hematogenous?
# Bacterial distribution of fracture-related infections

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>30-42%</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>20-39%</td>
</tr>
<tr>
<td>Enterobacteriaceae*</td>
<td>14-27%</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>16%</td>
</tr>
<tr>
<td>Streptococci</td>
<td>11%</td>
</tr>
</tbody>
</table>

*: MDR GNB especially in polytrauma patients with prolonged ICU stay
Biofilm
Biofilm

- Antibiotic diffusion
- Phagocytes/Complement diffusion
- Stationary growth phase
- Intracellular position
- Protein concentration
- Enzymes production
- Bacterial inoculum
- Mutation rates

Reduced activity of most antibiotics; surgery is needed
Persisting microorganisms

Intracellular survival

Biofilm formation

S. aureus

Osteoblast

Osteocyte

Osteoclast

Implant

Slide from Dr J Josse
S. aureus infection increases osteoclastic activity
Role of antibiotics

• To help complete the scheduled surgical plan!
• The main goal of the management strategy is FUSION
• Infection remission is a secondary (but welcome!) objective

• 2 distincts aspects of the antimicrobial treatment:
  • To help surgeons conduct the surgical plan (i.e., combat evident infection-pus, tissue damage including bone necrosis= extra cellular microorganisms in exponential growth phase)
  • To prevent any recurrent infection (i.e., combat « persisters microorganisms» = biofilm and intracellular cells)
Management strategies

• Acute infection (\(\text{? One month}\))
  • Debridement antibiotics and implant retention (DAIR)

• Chronic infection
  • Implant replacement (+/- bone reconstruction)
    • One-stage
    • Two-stage
  • Retention of the infected implants
### Management strategies

<table>
<thead>
<tr>
<th>Acute infection (? One month)</th>
<th>Fracture healed?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Debridement antibiotics and implant retention (DAIR)</td>
<td>• Yes</td>
</tr>
<tr>
<td>• Chronic infection</td>
<td>• No</td>
</tr>
<tr>
<td>• Implant replacement (+/- bone reconstruction)</td>
<td>• Implant replacement (1/2 stage) = antibiofilm Abx (ERADICATION)</td>
</tr>
<tr>
<td>• One-stage</td>
<td>• Implant retention = DAIR ± SAT (ERADICATION ± SUPPRESSION)</td>
</tr>
<tr>
<td>• Two-stage</td>
<td></td>
</tr>
<tr>
<td>• Retention of the infected implants</td>
<td></td>
</tr>
</tbody>
</table>

• Acute infection (? One month): Debridement, antibiotics, and implant retention (DAIR).

• Chronic infection:
  - Implant replacement (+/- bone reconstruction)
    - One-stage
    - Two-stage
    - Retention of the infected implants

• Fracture healed?
  - Yes: Implant removal = treatment of (chronic?) osteomyelitis (ERADICATION)
  - No: Implant replacement (1/2 stage) = antibiofilm Abx (ERADICATION)
Simples rules

- Antibiotic-free period prior to any interventions (except in case of emergency)
- Reliable (i.e., deep, “no touch” technique, change of the instruments, multiple) samples during each (re)intervention
- Empirical peroperative broad-spectrum antibiotics in every intervention with debridement and retention of the infected implants or implant insertion
- Multidisciplinary discussion BEFORE the intervention is done!
Surgery (DAIR, 1 stage or 2\textsuperscript{nd} intervention of a 2 stage replacement)

Peroperative sample\textbf{S}

Peroperative empirical antibiotic therapy debuted after sampling:
- bactericidal
- broad spectrum
- IV, high doses

\textbf{« no touch »} technique
Sterile surgical tools

No antibiotic prophylaxis (?)

No previous antibiotic treatment in the 2 weeks before (if feasible)

D0

D5-14

Antibiotic therapy targeted to the sample culture results:
- active in biofilm (DAIR/1StR)
- narrow spectrum
- high oral bioavailability
Per-operative (empiric) antibiotic treatment

- **Gram Positive Cocci**
  - staphylococci (including MR)
    - *S. aureus*
    - CoNS
  - streptococci/enterococci
  - strict anaerobes *

- **Gram Negative Bacilli**
  - Enterobacteriaceae
    - *P. aeruginosa*
  - other

- **Anaerobes**

- **Fungi**

  - **Vancomycin**
  - Teicoplanin (weak coverage of CoNS)
  - Linezolid* Tedizolid*
  - Tigecyclin*
  - Daptomycin
  - Ceftaroline, Ceftobiprole

  - **Piperacillin-tazobactam**
  - Ticarcillin-clavulanic acid
  - Imi/Mero-penem
  - (Ceftolozane-tazobactam, Ceftazidime-avibactam)

  - **Echinocandin**

* : active against anaerobes but only bacteriostatic
# Antibiotics bone concentration

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC (mg/liter)</th>
<th>Usual plasmatic concn (mg/liter)</th>
<th>Usual bone/plasma ratio</th>
<th>Conc (mg/liter)$^b$</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$C_{\text{min}}$</td>
<td>$C_{\text{bone}}$</td>
</tr>
<tr>
<td><strong>Beta-lactams</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxacillin</td>
<td>0.094</td>
<td>50</td>
<td>0.17</td>
<td>3.33</td>
<td>10</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>0.19</td>
<td>20</td>
<td>0.19</td>
<td>1.33</td>
<td>4</td>
</tr>
<tr>
<td><strong>Clindamycin</strong></td>
<td>0.032</td>
<td>4—14</td>
<td>0.35</td>
<td>1.33</td>
<td>4</td>
</tr>
<tr>
<td><strong>Fosfomycin</strong></td>
<td>2</td>
<td>4—14</td>
<td>0.35</td>
<td>1.33</td>
<td>4</td>
</tr>
<tr>
<td><strong>Glyco/lipopeptides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1.5</td>
<td>20—40</td>
<td>0.21</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>1.5</td>
<td>10—70</td>
<td>0.21</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>0.19</td>
<td>4—11</td>
<td>0.24</td>
<td>1.7</td>
<td>5</td>
</tr>
<tr>
<td><strong>Linezolid</strong></td>
<td>1</td>
<td>20</td>
<td>0.4</td>
<td>2.67</td>
<td>8</td>
</tr>
<tr>
<td>Ofl oxacin</td>
<td>0.5</td>
<td>5</td>
<td>0.5</td>
<td>0.67</td>
<td>2</td>
</tr>
<tr>
<td>Rifampin</td>
<td>0.004</td>
<td>10—30</td>
<td>0.27</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>0.125</td>
<td>0.2—1.5</td>
<td>0.35</td>
<td>0.1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Antibiotic concentrations in Diabetic Foot Osteomyelitis

- Fosfomycin (1)
- Daptomycin (2)
- Linezolid (3)

Antibiotics intraosteoelastic concentration

Valour F et al. AAC 2015
Rifampicin

- Sustained activity in staphylococcal biofilms
- Active against MRSA and MRSE
- Almost 100% oral bioavailability
- Numerous studies showing its efficacy in both clinical, in vivo and in vitro experimental studies:
  - Drancourt. J Antimicrob Chemother 1997; 39: 235–240, etc...

- Limits:
  - never use as monotherapy
  - never use in empirical treatment
  - no place in acute (fever, bacteremia, large inocula, ..)
  - tolerance, drug-drug interactions
## Fluoroquinolone Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Dosage (mg)</th>
<th>PO /j</th>
<th>C_{max} (mg/l)</th>
<th>oral BD (%)</th>
<th>t1/2 (h)</th>
<th>D Vol (l/kg)</th>
<th>Renal Elim. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>400</td>
<td>2 x</td>
<td>1.6</td>
<td>50%</td>
<td>4-5</td>
<td>1.5</td>
<td>25-40</td>
</tr>
<tr>
<td>Pefloxacine</td>
<td>400</td>
<td>2 x</td>
<td>4.6</td>
<td>&gt;90%</td>
<td>10</td>
<td>1.5-2.0</td>
<td>30-60</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500</td>
<td>2 x</td>
<td>1.5</td>
<td>60-80%</td>
<td>3-5</td>
<td>2.5-5.0</td>
<td>30-50</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400</td>
<td>2 x</td>
<td>3.1</td>
<td>85-95%</td>
<td>5-7</td>
<td>1.2</td>
<td>70-85</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500</td>
<td>1 x</td>
<td>8.7</td>
<td>&gt;90%</td>
<td>6-8</td>
<td>0.5</td>
<td>85-90</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400</td>
<td>1 x</td>
<td>3.6</td>
<td>90%</td>
<td>10</td>
<td>2</td>
<td>20-30</td>
</tr>
</tbody>
</table>
Predictors of outcome in DAIR approach for staphylococcal PJIs: rôle of rifampicin combinations

Zimmerli W. JAMA 1998; 279:1537
Senneville E. Clin Infect Dis 2011; 53: 334
Predictors of outcome in DAIR approach for staphylococcal PJIs: rôle of rifampicin fluoroquinolone combinations

Puhto AP et al. Int Orthop 2015
Antibiotic regimens for staphylococci implant-associated bone infections

1\textsuperscript{st} choice:
\begin{itemize}
  \item rifampicin + [levofloxacin or doxy/minocycline or TMP-SMX or line/tedizolide or fusidic acid]
  \item rifampicine + [daptomycine or teicoplanine or tigecycline or dalbavancine]
\end{itemize}

2\textsuperscript{nd} choice [if rifampicin is contraindicated (resistance, tolerance)]:
\begin{itemize}
  \item line/tedizolide monotherapy
  \item daptomycine + [levofloxacin or doxy/mino/tigecycline or TMP-SMX or fusidic acid]
\end{itemize}

French National Center for Complex Bone and Joint Infections North-West Region (CRIOAC Lille-Tourcoing)
Predictors of outcome in DAIR approach for GNB PJIs: role of fluoroquinolone combinations

D. Rodríguez-Pardo et al. Clin Microb Infect 2014
Antibiotic regimens for GNB implant-associated bone infections

1\textsuperscript{st} choice:
- Cefepime or any active BL agent + (levofloxacin or ciprofloxacin) 1 to 3 weeks
- then FQ monotherapy

2\textsuperscript{nd} choice [if FQ contraindicated (resistance, tolerance)]:
- Cefepime or any active BL agent + (colistin, doxy/mino/tigecycline, fosfomycin, aminoglycoside)
- Any active agent in case of multiresistance (cefiderocol??, bacteriophages, ...)

French National Center for Complex Bone and Joint Infections North-West Region (CRIOAC Lille-Tourcoing)
Oral versus intravenous antibiotic therapy

- **2012 IDSA Guidelines :**
  - Staphylococcal PJI with debridement :
    « Two to 6 weeks of [...] intravenous antimicrobial therapy [...]”
  - Other organisms PJI with debridement :
    “Four to 6 weeks of intravenous or highly bioavailable oral antimicrobial therapy”
  - PJI following resection arthroplasty :
    “Four to 6 weeks of intravenous or highly bioavailable oral therapy.”

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Oral bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin</td>
<td>90-100%</td>
</tr>
<tr>
<td>Linezolid</td>
<td>95-100%</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>90%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>90%</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>90-95%</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>85%</td>
</tr>
</tbody>
</table>
Oral versus intravenous antibiotic treatment for bone and joint infections (OVIVA): study protocol for a randomised controlled trial

Eligible for trial and has completed seven days or less of IV treatment

- Informed Consent
- Randomise

IV treatment, individual antibiotic chosen based on bacteria likely to be present

- Tailored IV treatment based on lab results
- Monitor progress, but antibiotic choice not influenced by study.

PO treatment, individual antibiotic chosen based on bacteria likely to be present

- Tailored PO treatment based on lab results

Culture results awaited.

Culture results available.

First six weeks
Oral versus parenteral antibiotic therapy for bone and joint infections: OVIVA study

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Oral Group</th>
<th>Intravenous Group</th>
<th>Risk Difference (90% CI; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat population</td>
<td>70.0/527</td>
<td>77.3/527</td>
<td>−1.4 (−4.9 to 2.2; −5.6 to 2.9)</td>
</tr>
<tr>
<td>Modified intention-to-treat population</td>
<td>67/509</td>
<td>74/506</td>
<td>−1.5 (−5.0 to 2.1; −5.7 to 2.8)</td>
</tr>
<tr>
<td>Per-protocol population</td>
<td>61/466</td>
<td>69/443</td>
<td>−2.5 (−6.3 to 1.3; −7.0 to 2.1)</td>
</tr>
<tr>
<td>Worst-case sensitivity analysis</td>
<td>85/527</td>
<td>74/527</td>
<td>2.1 (−1.5 to 5.7; −2.2 to 6.4)</td>
</tr>
</tbody>
</table>

Li HK et al. NEJM 2019
Oral Antibiotic treatment?
Epidemiology of infected Diabetic Foot Ulcers in a tertiary hospital in India

Antibiotic Susceptibilities

Saseedharan S et al. BJ Microb 2018
Conclusions

- The principles established for the management of PJIs may apply to Fracture-Related Infections (FRIs)
- Fracture healing is THE main goal
- Plans should be discussed BEFORE any surgical decision regarding the indication and the choice of the antibiotic treatment
- Again and again: tailored case management in a MULTIDISCIPLINARY setting
- Place of new agents against persisters?
What do you mean "left leg"?