Periprosthetic Joint infection
“PJI”

J. Geurts

Dept. Orthopaedic Surgery, MUMC+, the Netherlands
DISCLOSURE

No disclosures relevant to this presentation
The bionic society
Quality of life!!
Overview

- Definition
- Management
- Biofilm = enemy
- Challenges
- Future trends
• Deep PJI is one of the most common causes for implant failure and revisions, with dramatic medical and socioeconomic implications.

• PJI is a tremendous burden for individual patients as well as global health care

• Appropriate recognition and management are critical to preserve/restore function and prevent excessive morbidity.
Projections of Primary and Revision Hip and Knee
Arthroplasty in the United States from 2005 to 2030.
Kurtz, Steven; Ong, Kevin; Lau, Edmund; Mowat, Fionna;
Halpern, Michael; MPH, MD
DOI: 10.2106/JBJS.F.00222
Swedish Hip registry 2016

By 2030 over 60% of all total joint revisions will be because of PJIs.
The Impact of Infection After Total Hip Arthroplasty on Hospital and Surgeon Resource Utilization

Kevin J. Bozic and Michael D. Ries


<table>
<thead>
<tr>
<th></th>
<th>Group 1 (Revision Arthroplasty for Infection)†</th>
<th>Group 2 (Revision Arthroplasty for Aseptic Loosening)†</th>
<th>Group 3 (Primary Arthroplasty)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 29)</td>
<td>(N = 27)</td>
<td>(N = 29)</td>
</tr>
<tr>
<td>No. of hospitalizations</td>
<td>3.6 ± 2.1</td>
<td>1.2 ± 0.5</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Total no. of days in hospital</td>
<td>28.2 ± 20.9</td>
<td>8.1 ± 5.3</td>
<td>6.2 ± 2.4</td>
</tr>
<tr>
<td>Total no. of operations</td>
<td>3.690 ± 2.222</td>
<td>1.407 ± 0.888</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Total hospital costs (US$)</td>
<td>96,166 ± 60,664</td>
<td>34,866 ± 15,547</td>
<td>21,654 ± 4291</td>
</tr>
<tr>
<td>No. of outpatient visits</td>
<td>54.6 ± 35.1</td>
<td>20.8 ± 8.6</td>
<td>21.8</td>
</tr>
<tr>
<td>Total outpatient charges (US$)</td>
<td>48,348 ± 27,965</td>
<td>16,411 ± 9478</td>
<td>8519 ± 4185</td>
</tr>
</tbody>
</table>

*Note:* The numbers in the table indicate the average values with standard deviations. The highlighted values indicate a significant difference in resource utilization between groups.
Definition by MSIS

Definite PJI exists when:

**Major**
- There is a sinus tract communication with the prosthesis; or
- A pathogen is isolated by culture from at least 2 separate tissue or fluid samples, obtained from the affected prosthetic joint; or

**Minor**
- 4 of following 6 criteria exist:
  1. Elevated ESR and CRP concentration,
  2. Elevated synovial leucocyte count,
  3. Elevated synovial neutrophil percentage (PMN%),
  4. Presence of purulence in the affected joint,
  5. Isolation of a microorganism in 1 culture of periprosthetic tissue or fluid,
  6. >5 neutrophils per HPF in 5 HPF’s observed from histologic analysis of periprosthetic tissue at x400

Three types of implant infection

<table>
<thead>
<tr>
<th>Time</th>
<th>0–2 months</th>
<th>3–24 months</th>
<th>Any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Early postoperative</td>
<td>Delayed (low grade)</td>
<td>Late</td>
</tr>
<tr>
<td>Route</td>
<td>Perioperative</td>
<td>Haematogenous</td>
<td></td>
</tr>
<tr>
<td>Signs</td>
<td>Fever, effusion, warmth, drainage</td>
<td>Persistent pain, device loosening, fistula</td>
<td>Acute or subacute</td>
</tr>
<tr>
<td>Cause</td>
<td>S. aureus Streptococci Enterococci</td>
<td>Coagulase-negative staphylococci P. acnes</td>
<td>S. aureus E. coli</td>
</tr>
</tbody>
</table>

Zimmerli W NEJM 2004 Trampuz A Injury 2006
Definition

- **Superficial**
  - Skin
  - Subcutaneous Tissue
  - Deep Soft Tissue (fascia & muscle)
  - Organ/Space

- **Deep**
  - Superficial Incisional SSI
  - Deep Incisional SSI
  - Organ/Space SSI
Treatment strategies

- In situ treatment: DAIR: debridement, antibiotics & implant retention
- One-step exchange
- Two-step exchange
- Definitive removal: Girdlestone / arthrodesis
- Long-term suppressive antibiotic therapy
Treatment infected TJA

Debridement and retention

Onset of infection

Debridement

2–4 weeks i.v.

8–10 weeks p.o.

Explantation and implantation

One stage

Explantation

Implantation

Two stage (short interval)

Explantation

Implantation

“Biofilm treatment” (with rifampin)

Two stage (long interval)

Explantation

6 weeks i.v.

(2 weeks)

“Osteomyelitis treatment” (no rifampin)


Borens O et al. Rev Med Suisse 2009
Treatment concept: Surgery and Antibiotics
Error: antibiotic treatment without surgery

- Cure rate 8%
- Cure rate 9%

What are we fighting? BIOFILM!

- One of the most resistant forms of life on Earth
- Most bacteria in nature live in biofilm communities

Hot, acidic pools in Yellowstone National Park

Glaciers in Antarctica
What are we fighting? BIOFILM!

- Dynamic concept
- Reduced antimicrobial susceptibility
  - Low growth rate
  - “persisters”
  - Micro-environment that impairs antimicrobial activity
- Bacteriae also protected from host immune system
Biofilm: The race for the surface

1 min    3 h    12 h    1 day    3 days

Gristina AG. Biomaterial-centered infection: microbial adhesion versus tissue integration. Science 1987;237:1588-95
Biofilm: The race for the surface

Microbial adhesion and biofilm formation compete with tissue integration of host

Bacteria win ➔ formation biofilm on implant

Bacteria win ➔ infection risk <

Tissue cells win

Biofilm: The race for the surface

2 h incubation

12 h incubation
Biofilm: The race for the surface

Bacteria attached to biomaterials are securely anchored and hardly reachable for immune response cells and antibiotics.

- Polymers: predeposition for *st.epidermidis*
- Metals: predeposition for *st.aureus*

Relative risk: CrCo > stainless steel > titanium

Biomaterials infections are hard to treat.

Eventually implant removal may be necessary.
Biofilm Challenges

**Diagnostics**

- With joint aspiration/swabs/tissue cultures we find planktonic bacteria
- We cannot remove biofilm bacteria
- Sensitivity is not high enough!
Biofilm Challenges

Diagnostics

• Sonication
Results of sonication study

846 implants
(367 joint prostheses + 479 fracture fixation devices)

<table>
<thead>
<tr>
<th>Microbiologic test</th>
<th>Aseptic cases (n = 675)</th>
<th>Infected cases (n = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue culture</td>
<td>26 (4%)</td>
<td>126 (74%)</td>
</tr>
<tr>
<td>Sonicate culture</td>
<td>30 (5%)</td>
<td>152 (89%)</td>
</tr>
</tbody>
</table>

Problem: still high numbers of false positive and false negative

Biofilm Challenges

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sonication</td>
<td>• Risk of contamination : multi-step procedure</td>
</tr>
<tr>
<td></td>
<td>• Operator dependent procedures</td>
</tr>
<tr>
<td></td>
<td>1. Harvesting of samples in operation</td>
</tr>
<tr>
<td></td>
<td>2. Transport of harvested samples to lab</td>
</tr>
<tr>
<td></td>
<td>3. Inserting physiological solution in container</td>
</tr>
<tr>
<td></td>
<td>4. Sonicating the samples</td>
</tr>
<tr>
<td></td>
<td>5. Collecting the fluid after sonication</td>
</tr>
<tr>
<td></td>
<td>6. Centrifuging the fluid</td>
</tr>
<tr>
<td></td>
<td>7. Culturing bacteria pellet in solid media or broth</td>
</tr>
</tbody>
</table>
Biofilm Challenges

**Diagnostics**

- Sonication

**Problems**

- Gram -
Biofilm Challenges

Diagnostics

• Dislodging of biofilm
  DTT : dithiotreitol → to dissolve the polysaccharide matrix of the biofilm and detach the bacteriae
Biofilm Challenges

Diagnostics

• DTT

Use of Dithiothreitol to Improve the Diagnosis of Prosthetic Joint Infections

Methods: Periprosthetic tissue samples (n=5-8). Removed implants aseptically divided into two parts and transported to the laboratory and randomly processed by sonication or DTT. Diagnosis of infection according Spanghel criteria

<table>
<thead>
<tr>
<th>Results</th>
<th>Tissue Cultures</th>
<th>Sonication</th>
<th>DTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>71.4%</td>
<td>71.4%</td>
<td>85.7%</td>
</tr>
<tr>
<td>Specificity</td>
<td>76.5%</td>
<td>94.1%</td>
<td>94.1%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>78.9%</td>
<td>93.7%</td>
<td>94.7%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>68.4%</td>
<td>72.7%</td>
<td>84.2%</td>
</tr>
</tbody>
</table>
Biofilm Challenges

Diagnostics

- PCR
- MALDI-TOF
- Calorimetry

→ Pathogen identification <24h
Biofilm Challenges

Treatment

• GOAL =
  • Reduce bacterial load
  • Breakdown of biofilm in order to force bacteriae in planktonic state and make them susceptible

• Ways to do this =
  • Do it early
  • Change all modular parts
  • Mechanically disrupt biofilm
Biofilm Challenges

Treatment

• DAIR : time is running and biofilm is coming fast
  • Succes-rate DAIR ↓

  • With time (4w : 90%, 8w : 80%, > 8w : 50%)
  • Deterioration of soft tissue
  • “difficult-to-treat” bacteria : resistance / high MIC
    eg. Enterococcus : never DAIR

  • After revision
Biofilm Challenges

Treatment

• DAIR

CHANGE THE MODULAR PARTS!

Polyethylene Insert Exchange Is Crucial in Debridement for Acute Periprosthetic Infections following Total Knee Arthroplasty


Cure rate 93% versus 30% (p=0.0001)
Biofilm Challenges

Treatment: CHANGE THE MODULAR PARTS!

Oxford study

- Exchange modular parts: 10y survival  86% vs 68% (p=0.02)

- Combi:
  - Early + exchange: 90% (78-100%)
  - Early + no exchange: 81% (67-95%)
  - Late + exchange: 79% (60-98%)
  - Late + no exchange: 52% (31-73%)
Biofilm Challenges

Treatment: DISRUPTION OF BIOFILM
Biofilm Challenges

Treatment

DISRUPTION OF BIOFILM
Other Challenges; Cultures

• Instruct your orthopaedic surgeon!

• Separate instruments

• Obtain ≥ 3 tissue specimens

• No-touch technique

• No swabs, no sinus tract cultures
Other Challenges; Antibiotics

- AB’s are not anti-inflammatory drugs → should not be given to combat erythema
- Never give AB unless infection is confirmed and adequate work-up performed
- Systemic AB
  - AB in the wrong way (oral monotherapy with AB with low bio-availability; penicillin, …)
  - Rifampicin: no rifa / rifa monotherapy / …
  - AB too long / too short
### Other Challenges; Antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral bioavailability</th>
<th>Bone penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/clavulanic acid or ampicillin/sulbactam</td>
<td>15% (AUC 6x lower with PO dose)</td>
<td>7%</td>
</tr>
<tr>
<td>Cefuroxim, cefadroxil</td>
<td>10% (AUC 10x lower with PO dose)</td>
<td>12%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>70%</td>
<td>48%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>100%</td>
<td>77%</td>
</tr>
<tr>
<td>Rifampin</td>
<td>80%</td>
<td>51%</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>85%</td>
<td>55%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>90%</td>
<td>45%</td>
</tr>
</tbody>
</table>
Other Challenges ; Antibiotics

Risk factors for rifampicin resistance

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n = 48)</th>
<th>Controls (n = 48)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated with any antibiotics</td>
<td>44 (91.7 %)</td>
<td>30 (62.5 %)</td>
<td>0.001f</td>
</tr>
<tr>
<td>Treated with rifampin</td>
<td>41 (85.4 %)</td>
<td>20 (41.7 %)</td>
<td>&lt;0.001f</td>
</tr>
<tr>
<td>Rifampin always adequateb</td>
<td>25</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Rifampin inadequate</td>
<td>16</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Monotherapy and/or</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Empiric therapyc and/or</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other reasonsd</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Treatment with high bacterial load</td>
<td>34 (70.8 %)</td>
<td>13 (27.1 %)</td>
<td>&lt;0.001f</td>
</tr>
<tr>
<td>&lt;2 weeks iv antimicrobial treatment</td>
<td>12</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>No surgical debridement</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No iv and no surgical debridement</td>
<td>15</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Other Challenges ; Soft tissue management

If you don’t solve the problem…
• Iatrogenic fistula
• Longterm VAC treatment

Inadequate soft tissue management will lead to
• Superinfection
• Multiresistant pathogens
Other Challenges; Soft tissue management

High bacterial load in negative pressure wound therapy (NPWT) foams used in the treatment of chronic wounds

Erlangga Yusuf MD, PhD, Xavier Jordan MD, Martin Clauss MD, Olivier Borens MD, Mark Mader MD, PhD, Andrej Trampuz MD

Probably no indication for use of VAC in bone/implant infections
Other Challenges; Spacer contamination

• Over time: biofilm can & will form on spacers

Staphylococcus aureus biofilm formation on different gentamicin-loaded polymethylmethacrylate bone cements
Hilbrand van de Belt a, b, Daniëlle Neut a, b, Willem Schenk a, Jim R van Horn a, Henny C van der Mei b, Henk J Busscher b,  d,  e

• Possibly induction of resistant strains
Future trends

Anti-infection coatings

<table>
<thead>
<tr>
<th>Requirements</th>
<th>Fulfillments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>No systemic toxicity</td>
</tr>
<tr>
<td></td>
<td>No local toxicity</td>
</tr>
<tr>
<td></td>
<td>No detrimental effects on bone healing</td>
</tr>
<tr>
<td></td>
<td>No unwanted long-term side effects</td>
</tr>
<tr>
<td>In vitro activity</td>
<td>No cytotoxicity or genotoxicity</td>
</tr>
<tr>
<td></td>
<td>Proven bactericidal and antibiofilm activity on different surfaces</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Proven in vivo</td>
</tr>
<tr>
<td></td>
<td>Case series</td>
</tr>
<tr>
<td>Ease-of-use</td>
<td>Easy handling</td>
</tr>
<tr>
<td></td>
<td>Versatility</td>
</tr>
<tr>
<td>Market</td>
<td>Acceptable cost</td>
</tr>
<tr>
<td></td>
<td>Large availability</td>
</tr>
<tr>
<td></td>
<td>Easy to manufacture</td>
</tr>
<tr>
<td></td>
<td>Overcomes regulatory issues</td>
</tr>
</tbody>
</table>

Antibacterial coating of implants in orthopaedics and trauma: a classification proposal in an evolving panorama

Carlo Luca Romanò, Sara Scarponi, Enrico Gallazzi, Delia Romanò, and Lorenzo Drago
Future trends

Anti-infection coatings

• Au, Ag,…
Future trends

Anti-infection coatings

- Biomolecular coatings
  - cfr Hydrogel: hyaluronic acid + polylactic acid (DAC®)
Future trends

Not addressed in this talk:

• Prevention
• Diagnostics
• Imaging
So let’s join forces and battle this challenge together

microbiology ➔ ortho