Persistance bactérienne au cours des IOA

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Division of Infectious Diseases
University Hospital Lausanne, Switzerland
Implants: improve function or replace missing anatomic structure
## Risk of implant-associated infection

<table>
<thead>
<tr>
<th>Device</th>
<th>No. inserted in the US per year</th>
<th>Rate of infection, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture fixation devices</td>
<td>2,000,000</td>
<td>5–10</td>
</tr>
<tr>
<td>Dental implants</td>
<td>1,000,000</td>
<td>5–10</td>
</tr>
<tr>
<td>Joint prostheses</td>
<td>600,000</td>
<td>1–3</td>
</tr>
<tr>
<td>Vascular grafts</td>
<td>450,000</td>
<td>1–5</td>
</tr>
<tr>
<td>Cardiac pacemakers</td>
<td>300,000</td>
<td>1–7</td>
</tr>
<tr>
<td>Mammary implants</td>
<td>130,000</td>
<td>1–2</td>
</tr>
<tr>
<td>Mechanical heart valves</td>
<td>85,000</td>
<td>1–3</td>
</tr>
<tr>
<td>Penile implants</td>
<td>15,000</td>
<td>1–3</td>
</tr>
<tr>
<td>Heart assist devices</td>
<td>700</td>
<td>25–50</td>
</tr>
</tbody>
</table>

Darouiche RO. *Clin Infect Dis* 2001;33:1567–1572
What to do?

- Stop performing implantations?
- Multiple mutilating surgeries?
- Aggressive tumor-like surgery?
- Amputation?

No
Debridement and retention

One stage

Two stage (short interval)

Two stage (long interval)

Onset of infection

2–4 weeks i.v.

8–10 weeks p.o.

Explantation and implantation

6 weeks i.v.

(2 weeks)


Borens O et al. Rev Med Suisse 2009

"Biofilm treatment" (with rifampin)

"Osteomyelitis treatment" (no rifampin)
Concept based on:

1. Teamwork
2. Understanding biofilm
3. Definition & classification
4. Diagnosis
5. Treatment: first treatment attempt!

Infection is the best possible complication
Key to success

How would you call two surgeons reading a microbiology result?
=> A double blind study

How would you call two Infectious Diseases physicians reading a surgical report?
=> A randomized study

How would you call two microbiologists discussing about the type of implant?
=> Expert opinion conference
Goal

- Functional and pain-free implant
  - Highly efficient concept (90% cure)
  - Least invasive (retention, whenever possible)
- Eradication of infection
  - Combination of surgery + antibiotics (bundle)
  - Not antibiotic suppression (whenever possible)
- Scientific evidence
  - In vitro
  - Animal models
  - Clinical studies

What do we know?
Understanding biofilm
Interactions

- Host
  - Bio-compatibility
  - MIC/MBC, MOA
  - Susceptibility
  - Tissue response

- Drug
  - PK: Absorption, distribution, metabolism, elimination
  - PD: toxicity, side effects
  - Mechanical-physical properties
  - Release kinetics, chemical compatibility, drug degradation

- Pathogen
  - Virulence factors, biofilm formation
  - Immune system
  - Antibacterial activity (coating, nanostructure)
  - Bacterial adhesion, biofilm formation, integration

- Material
  - Mechanical-physical properties
  - Release kinetics, chemical compatibility, drug degradation

Biofilms: life on surfaces

- Most bacteria in nature live in biofilms
- One of the most resistant forms of life

Hot, acidic pools in Yellowstone National Park

Glaciers in Antarctica
Evolution of life on Earth

- 2.5 billion years ago: Cyanobacteria form biofilms
- 3.5 billion years ago: First life forms
- 4.6 billion years ago: Development of Earth
## Evolution of life

100 years = 1 second

<table>
<thead>
<tr>
<th>Organism</th>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>January 1</td>
<td>00:00</td>
</tr>
<tr>
<td>Fungi</td>
<td>June 18</td>
<td>04:48</td>
</tr>
</tbody>
</table>
Biofilm: characteristics

- Adherent to surface (min-h)
- Embedded in matrix (70%)
- Slowly replicating (stationary-growth)
# Pathogenesis of foreign-body infection

<table>
<thead>
<tr>
<th>References (model)</th>
<th>Foreign body (FB)</th>
<th>Min. infectious dose</th>
<th>Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elek 1957 (human)</td>
<td>Sutures</td>
<td>$5 \times 10^6$</td>
<td>S. aureus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$3 \times 10^2$</td>
<td></td>
</tr>
<tr>
<td>James 1961 (mice)</td>
<td>Sutures</td>
<td>$10^6$</td>
<td>S. aureus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$&lt;10^3$</td>
<td></td>
</tr>
<tr>
<td>Zimmerli 1982 (guinea pigs)</td>
<td>Cages</td>
<td>$&gt;10^7$</td>
<td>S. aureus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$10^2$</td>
<td></td>
</tr>
<tr>
<td>Widmer 1988 (guinea pigs)</td>
<td>Cages</td>
<td>$&gt;10^7$</td>
<td>S. epidermidis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$10^3$</td>
<td></td>
</tr>
</tbody>
</table>
**Classification**

<table>
<thead>
<tr>
<th>Time after implantation</th>
<th>0–3 months</th>
<th>3–24 (36) months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of infection</strong></td>
<td>Early postoperative</td>
<td></td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>Haematogenous</td>
<td></td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td>Acute or subacute</td>
<td>Persistent loosening, fistula</td>
</tr>
<tr>
<td><strong>Pathogen</strong></td>
<td>S. aureus</td>
<td>E. coli</td>
</tr>
<tr>
<td></td>
<td>Enterococci</td>
<td>Coagulase-negative staphylococci</td>
</tr>
<tr>
<td></td>
<td>S. aureus</td>
<td>P. acnes</td>
</tr>
</tbody>
</table>

*4th group: Wrongly treated*
Crossing the borders of disciplines

Perception of the problem
- Surgeons: Personal failure (denial)
- ID specialists: Philosophy (unhelpful)
- Microbiologists: Lost (far clinical problem)

Approach to the problem
- Surgeons: Strong personal opinion
- ID specialists: Difficulties in communication
- Microbiologists: Focus on planktonic bacteria
Do we want to diagnose infection?

Ostriches bury their heads in the sand to avoid danger (legend).

Avoid an apparently risky situation by pretending it doesn’t exist (not legend).
Implant infections can be treated with antibiotics ONLY
Mechanical reduction of bacterial load

- Antibiotic
- No surgery
- Insufficient debridement
- Extensive debridement (+/- local antibiotics)

Bacterial count (log)

Time
Surgeon’s dogma

Implant infections can ONLY be cured with device removal
Antibiotics today

History of rifampicin

- Inhibits DNA-dependent RNA polymerase.

- 1957: A new substance was discovered in Milan from the soil of French Riviera, produced by *Streptomyces mediterranei* (now *Amycolatopsis rifamycinica*).

- 1959: A new semi-synthetic molecule was produced (today "rifampicin" = “rifampin”).
Foreign-body infection (FBI) model

- 4 Teflon cages implanted subcutaneously in guinea pigs
- Aspiration of cage fluid (planktonic bacteria)
- Cages removed 5 days after treatment (eradication)

# Efficacy in the guinea pig infection model (MRSA)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cure rate, %</th>
<th>Rifampin resistance rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>RIF (12.5)</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>VAN (15)</td>
<td>0%</td>
<td>58%</td>
</tr>
<tr>
<td>VAN (15) + RIF</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>LEV (10)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>LEV (10) + RIF</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>LIN (50)</td>
<td>0%</td>
<td>17%</td>
</tr>
<tr>
<td>LIN (50) + RIF</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>DAP (20)</td>
<td>0%</td>
<td>17%</td>
</tr>
<tr>
<td>DAP (20) + RIF</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>DAP (30)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>DAP 30 + RIF</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>DAP 40</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>DAP 40 + RIF</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

CURRENT CONCEPTS

Prosthetic-Joint Infections

Werner Zimmerli, M.D., Andrej Trampuz, M.D., and Peter E. Ochsner, M.D.
Surgical and antibiotic treatment concepts

Debridement and retention

Onset of infection

2–4 weeks i.v.

8–10 weeks p.o.

Debridement

Explantation and implantation

One stage

Explantation

Implantation

2 weeks

Two stage (short interval)

Explantation

Implantation

6 weeks i.v.

Two stage (long interval)

Explantation

Implantation

(2 weeks)

“Biofilm treatment” (with rifampin)

“Osteomyelitis treatment” (no rifampin)


Borens O et al. Rev Med Suisse 2009
Debridement & retention

1. Stable prosthesis (no loosening)
2. Short duration of infection (<3 weeks)
3. Good soft tissues
4. No difficult-to-treat organism:
   - Rifampin-resistant staphylococci
   - Small-colony variants
   - Quinolone-resistant Gram-negative bacilli
   - Enterococci
   - Nutritionally variant (defective) streptococci (*Abiotrophia* and *Granulicatella*)
   - Fungi
Modern surgical / antibiotic concepts

- Rapid & sufficient debridement (no fear)
- Wound closure (no repeated washout)
- Soft tissue coverage (no VAC)
- Dead space management
- No antibiotics before proper surgical intervention and with open wound.
Controversies in management of PJI between North America and Europe

- North America
  - Standard: 2-stage exchange with long interval (6–8 weeks)
  - No rifampin – dogma that infection is not possible to eradicate without implant removal
  - Retention: life-long suppression of infection

- Europe
  - 4 surgical approaches according to situation (algorithm)
  - Early and aggressive revision to make salvage of the implant possible
  - Highest success with lowest invasiveness
Activity of fosfomycin and rifampin against MRSA in the guinea pig model

Highest cure rate with FOS+RIF (83%), which was superior to other RIF-combinations.

No *in vivo* emergence of FOS resistance was observed in mono- or combination therapy.

Mihailescu R et al. ECCMID 2012 (P 2062, Monday, April 2, 13.30-14:30)
Treatment of *E. faecalis* biofilms in the guinea pig foreign-body model

Low inoculum: $10^4$ cfu/cage
Duration of infection: 3 h
*P. acnes* in the guinea pig model

Pathogenesis of infection

*P. acnes* switches from planktonic to biofilm form and persists with high inoculum on cages for ≥50 days.

Treatment against adherent *P. acnes* in the guinea pig model

- No spontaneous cure
- Emergence of rifampin-resistance not observed
- None of the cure rates exceeded 50%
- Daptomycin + rifampin showed highest cure (42%)

DAP = daptomycin, RIF = rifampicin.
Number in brackets: No cages cleared from adherent bacteria/total number
Activity against ESBL-producing *E. coli* in the guinea pig model

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC</th>
<th>MBC\textsubscript{log}</th>
<th>MBC\textsubscript{stat}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tigecycline</td>
<td>0.25</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Colistin</td>
<td>0.25</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>0.12</td>
<td>0.12</td>
<td>8</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2</td>
<td>8</td>
<td>16</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.001

Corvec S et al. ICAAC 2011 (manuscript submitted)
High-dose daptomycin for PJI: ongoing phase II study

Prosthesis

Stable
Debridement and retention

Onset of infection

2 weeks i.v. daptomycin* 10 mg/kg + rifampin p.o.

Levofloxacin 2 x 500 mg
Co-trimoxazole 3 x 1 DS
Doxycycline 2 x 100 mg
Fusidic acid 3 x 500 mg

10 weeks p.o. antibiotics

+ rifampin

Loose
Two stage (short interval)

Explantation

2 weeks i.v. daptomycin* 10 mg/kg (no rifampicin)

Implantation

*Daptomycin is not licensed for the treatment of PJI
Common reasons for failure

Surgical
- No (late) surgery
- Arthroscopic instead open surgery (change of mobile parts)
- Retention attempt of loose prosthesis
- Prosthesis removal in early and hematogenous infection

Antimicrobial
- No highly-active bactericidal antibiotic (initial i.v.)
- Short duration (total 3 months)
- No rifampin for staphylococcal biofilms
- Rifampin with open wound, fistula or VAC
Type of surgical procedure (for hip or knee PJI)

Success (cure rate) >90%
Interval from explantation until reimplantation (for hip and knee PJI)

Success (cure rate) >90%
Duration of hospital stay (patients with hip or knee PJI)

Success (cure rate) >90%
Summary

1. Implant can be retained, if:
   - Stable (no loosening)
   - Short duration of symptoms (<3 weeks)
   - Good soft tissues (no fistula)
   - No difficult-to-treat organisms

2. In all other situations, implant must be removed
   - Short interval until re-implantation (2-4 weeks)

3. Antibiotics against biofilm:
   - Eradication (oral long-term treatment): rifampin for staphylococci, ciprofloxacin for gram-negative rods
   - Important to lower bacterial density
   - Loose implant cannot be retained
Collaborative Centres & Observerships

- Lausanne: Focus on implant-associated infections
  - Microbiology: New methods for biofilm detection
  - Infectious diseases: Current concepts and controversies

50 registered centres

University Hospital Lausanne

www.escmid.ch/ecc
Study Group on Implant-Associated Infections

ESGIAI Business Meeting
(Monday, April 2, 2012, 9:00-11:00, room 13 + 14)

1. European implant cohort study
   - Web-based case report form

2. Educational activity
   - Educational Workshops (ECCMID 2013, Berlin)

3. Guidelines
   - Prevention, diagnosis and treatment of implant-associated infections

4. Multicenter studies and collaborative projects
   - Collaboration with other ESCMID Study Groups and societies

www.implantinfections.com
European Implant Cohort Study (EICS)

• To evaluate and improve the treatment concept of prosthetic joint infections (PJI)
  • Standardized surgical and antimicrobial treatment algorithm

• To determine factors associated with:
  • Infection outcome (infection-free interval)
  • Joint function (range of motion, mobility, pain)

• To perform research projects
  • Clinical (outcome, definition, diagnostic)
  • Laboratory (microbiology, PK/PD, genetic)
European bone and joint infection society (EBJIS)

Montreux, Switzerland (www.ebjis2012.org)
September 20-22, 2012 (abstract deadline: 30 April 2012)
Research team Infectious Diseases

Bertrand Bétrisey
Elena Maiolo
Cyrine Belkhoja
Stéphane Corvec
Laura Rio
Ulrika Furustrand
Laura Sessa
Inês da Fonesca
Christen Ravn
University Hospital Lausanne, Switzerland

(andrej.trampuz@chuv.ch)
Safety and Efficacy of Moxifloxacin Monotherapy for Treatment of Orthopedic Implant-Related Staphylococcal Infections

Rafael San Juan,1* Ana García-Reyne,1 Pedro Caba,2 Fernando Chaves,3 Carlos Resines,2 Fernando Llanos,2 Francisco López-Medrano,1 Manuel Lizasoain,1 and Jose María Aguado1

Unit of Infectious Diseases,1 Department of Traumatology,2 and Department of Clinical Microbiology,3 University Hospital 12 de Octubre, Madrid, Spain

Received 7 January 2010/Returned for modification 12 January 2010/Accepted 14 September 2010

Observational descriptive study

All patients with orthopedic device-related infection due to quinolone-susceptible staphylococci

June 2006 to April 2009

FIG. 1. Kaplan-Meier estimates of the cumulative risk of failure after treatment with moxifloxacin.
### Results

<table>
<thead>
<tr>
<th>Description</th>
<th>No. (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosynthesis material</td>
<td>28 (58.3)</td>
</tr>
<tr>
<td>Hip prosthesis</td>
<td>9 (18.8)</td>
</tr>
<tr>
<td>Knee prosthesis</td>
<td>10 (20.8)</td>
</tr>
<tr>
<td>Shoulder prosthesis</td>
<td>1 (2.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timing of infection</th>
<th>No. (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early infection</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td>Late chronic infection</td>
<td>33 (68.8)</td>
</tr>
<tr>
<td>Late hematogenous infection</td>
<td>3 (6.3)</td>
</tr>
<tr>
<td>Finding in prosthetic joint revision</td>
<td>6 (12.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Etiology of infection</th>
<th>No. (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>33 (68.8)</td>
</tr>
<tr>
<td>CoNS</td>
<td>15 (31.2)</td>
</tr>
</tbody>
</table>

| Median (range) no. of days of i.v. antibiotic treatment | 12.6 (1-31) |
| Median (range) no. of days of oral moxifloxacin treatment | 78 (24-223) |

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>No. (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events with moxifloxacin treatment</td>
<td>3 (6.3)</td>
</tr>
<tr>
<td>Adverse events requiring moxifloxacin withdrawal</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td>Surgical debridement with or without implant removal</td>
<td>37 (77.1)</td>
</tr>
<tr>
<td>Retention of implant</td>
<td>21 (43.8)</td>
</tr>
</tbody>
</table>

| Median (range) no. of days of follow-up | 716 (102-1,613) |

<table>
<thead>
<tr>
<th>No. (% of patients) with global cure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Per ITT</td>
<td>38 (79.1)</td>
</tr>
<tr>
<td>All patients (n = 46)</td>
<td>38 (82.6)</td>
</tr>
<tr>
<td>Patients with implant retention (n = 20)</td>
<td>15 (71.3)</td>
</tr>
<tr>
<td>Patients with <em>S. aureus</em> infection (n = 33)</td>
<td>26 (78.8)</td>
</tr>
<tr>
<td>Patients with CoNS infection with global cure (n = 14)</td>
<td>12 (86)</td>
</tr>
</tbody>
</table>
Teamwork

Werner Zimmerli

Olivier Borens
Changing mind can be difficult and takes time
<table>
<thead>
<tr>
<th>No.</th>
<th>Tissue</th>
<th>Sonication</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>68%</td>
<td>90%</td>
</tr>
<tr>
<td>80</td>
<td>80%</td>
<td>90% (CDI)</td>
</tr>
<tr>
<td>90</td>
<td>70%</td>
<td>96% (PCR)</td>
</tr>
<tr>
<td>32</td>
<td>31%</td>
<td>44%</td>
</tr>
<tr>
<td>34</td>
<td>56%</td>
<td>81%</td>
</tr>
</tbody>
</table>

- Ascione T et al., Italy (P 1802)
- Oliva A et al., Italy (P 1360)
- Portillo ME et al., Spain (P1363)
- Stylianakis A et al., Greece (P 1362)
- Salles M et al., Brasil (P 1361)
Discussion: authors

Efficacies of moxifloxacin treatment:
- 80% for patients with at least 2 years of follow-up
- 71% for patients managed with implant retention

- **Quinolones:**
  - Good in vitro antistaphylococcal activity in biofilms
  - Increased treatment compliance by a single dose
  - Low rate of side effects (4.2%)
  - Low rate of interaction with other drugs

- **Rifampin:**
  - Not needed to treat staphylococcal OA infections
  - Protective effect on the emergence of quinolone-resistant staphylococci not necessary when more active antistaphylococcal quinolones administered
  - Increased risk of adverse effect and pharmacological interactions
Conclusion: reviewers

- 71% cure rate (with debridement and implant retention) does not reflect the better activity of moxifloxacin (compared to ciprofloxacin)
  - No good effect on biofilm for *Staphylococcus*
  - Suppression instead of eradication?
  - Short-time follow-up
  - Osteomyelitis treatment in 56,2%

- With rifampin, the cure rate would be probably close to 100%

- Randomized study needed before to change practice
Imaging studies

- Plain radiographs
  - Helpful to detect infection when studied serially over time after implantation
  - New subperiosteal bone growth and transcortical sinus tracts are specific for infection

**Cave:** Migration of implant and periprosthetic osteolysis can also occur without infection

- Bone scintigraphy with technetium-99m or labeled leucocytes has high sensitivity, but it lacks specificity for infection

S. aureus cage infection

Sterile inflammation

Kidney
Bladder

SPECT/CT (4 h after $^{99m}$Tc-PAMA-4, 20 μCi i.v.)

Baldoni D et al. 2009 (in preparation)
Low cure of debridement & retention

  - 60% cure rate at 2 years\(^1\)
  - 32% cure rate at 2 years\(^2\)
- Chiu FY, Chen CM. *Clin Orthop Relat Res* 2007;461:130–135
  - 30% cure rate, minimum 3-years follow up\(^3\)

1. Improper patient selection
2. Insufficient surgical debridement
3. No rifampin use for biofilms
### Staphylococcal PJI
(Mayo Clinic, Rochester, MN)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Parenteral therapy</th>
<th>Oral therapy initiated following the end of parenteral therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recommended</td>
<td>Alternative</td>
</tr>
<tr>
<td><strong>Oxacillin-resistant</strong></td>
<td>Vancomycin 15 mg/kg iv Q12hrs + rifampin 900 mg daily for 4 weeks</td>
<td><strong>Levofloxacin</strong> 750 mg daily + rifampin 900 mg daily followed by suppressive therapy with trimethoprim/sulfamethoxazole PO DS Q12hrs or minocycline 100 mg po Q12hrs</td>
</tr>
<tr>
<td></td>
<td>Linezolid b 600 mg po/iv Q12hrs + rifampin 900 mg daily</td>
<td></td>
</tr>
<tr>
<td><strong>Oxacillin-sensitive</strong></td>
<td>Cefazolin 1–2 g iv Q8hrs + rifampin 900 mg daily for 4 weeks</td>
<td><strong>Levofloxacin</strong> 750 mg daily + rifampin 900 mg daily followed by suppressive therapy with cephalexin 500 PO Q6hrs or Q8hrs or cefadroxil 500 mg Q12hrs</td>
</tr>
<tr>
<td></td>
<td>Vancomycin 15 mg/kg iv Q12hrs + rifampin 900 mg daily</td>
<td></td>
</tr>
</tbody>
</table>

- **a** Rifampin 900 mg BID or TID (300 mg BID in case of GI intolerance)
- **b** Daptomycin or Synercid can substitute linezolid (if contraindicated)
- **c** Given for a total of 6 months for TKA and 3 months for THA
- **d** Suppressive therapy for the life of the total joint arthroplasty

El Helou et al. EJCMID 2010
Staphylococcal PJI

El Helou et al. EJCMID 2010
Controversies
Orthopedic devices (n = 24)

Estimate of survival with debridement and retention (1999-2002)*

- Stable implant
- No sinus tract
- Short symptom duration (<3 weeks)
- Median follow up of 3.7 years (1.8–4.7 years)

*Infections included hip prostheses (n=14), knee prostheses (n=5), internal fixation (n=4) and an ankle prosthesis (n=1)

Timeline of antibiotic discovery

Natural origin
- Gentamicin
- Tetracycline analogues
- Clindamycin
- Amikacin
- Cephalosporins
- Clavulanic acid

Synthetic origin
- Ampicillin, penicillin analogues
- Methicillin
- Rifampicin
- Trimethoprim, metronidazole

Genomic, chemical library screening
- Oritavancin
- Telavancin
- Daptomycin
- Linezolid
- Other fluoroquinolones
- Erythromycin analogues
- Teicoplanin
- Ciprofloxacin
- Imipenem
- Aztreonam

Natural product screening
- Gentamycin
- Tobramycin
- Amikacin
- Cephalosporins
- Clavulanic acid
- Genomics, screening, crystallography, de novo design, natural product template
- 1940
- 1960
- 2000
- 1980

Fernandes P. *Nature Biotechnology* 2006;24:1497–1503
67-y: Increasing pain after knee implantation 1 year ago. Which preoperative test most accurately detects infection?

a) Serum C-reactive protein (CRP)
b) Synovial fluid Gram stain & culture
c) Synovial fluid leukocyte count & differentiation
d) Conventional x-ray
e) PET / CT scan
1. Type of infection => Surgery
   - Acute (early & hematogenous)
   - Delayed (low-grade)

2. Type of microorganism
   - Antibiotic against biofilm?
   - Difficult to treat

Daptomycin indications in Europe

- Daptomycin is approved for treatment of:
  - Complicated skin and soft tissue infection (cSSTI)
  - Right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*
  - *S. aureus* bacteraemia (SAB) when associated with RIE or cSSTI

Dosing recommendations for daptomycin

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dosing frequency</th>
<th>Approved doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30 ml/min</td>
<td>q24h</td>
<td>cSSTI: 4 mg/kg</td>
</tr>
<tr>
<td>&lt;30 ml/min*</td>
<td>q48h</td>
<td></td>
</tr>
</tbody>
</table>

*With or without dialysis. The same dose adjustments are recommended for patients on haemodialysis or continuous ambulatory peritoneal dialysis. Whenever possible, daptomycin should be administered following the completion of dialysis on dialysis days.

Daptomycin PK study in a guinea pig implant model

PK of daptomycin in sterile cage fluids after administration of single intraperitoneal doses of daptomycin

- $C_{\text{max}} > MBC_{\text{stat}}$
- $\text{AUC}_{0-24}$ dose-dependent
- $\sim 4, 6$ and $8 \text{ mg/kg}$ doses in humans

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>$C_{\text{max}}$ (µg/ml)</th>
<th>$C_{\text{min}}$ (µg/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>23.1 ± 7.0</td>
<td>1.5 ± 1.1</td>
<td>6.0 ± 2.0</td>
</tr>
<tr>
<td>30</td>
<td>46.3 ± 8.8</td>
<td>9.8 ± 2.9</td>
<td>4.7 ± 1.2</td>
</tr>
<tr>
<td>40</td>
<td>53.7 ± 1.3</td>
<td>4.1 ± 2.3</td>
<td>6.0 ± 0.0</td>
</tr>
</tbody>
</table>

## Microbiology

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative staphylococci (e.g. <em>Staphylococcus epidermidis</em>)</td>
<td>30%</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>20%</td>
</tr>
<tr>
<td>Streptococci &amp; enetrococci</td>
<td>10%</td>
</tr>
<tr>
<td>Gram-negative bacilli (e.g. <em>Escherichia coli</em>)</td>
<td>10%</td>
</tr>
<tr>
<td>Anaerobes (e.g. <em>Propionibacterium acnes</em>)</td>
<td>5-10%</td>
</tr>
<tr>
<td>Mixed infections</td>
<td>10-20%</td>
</tr>
<tr>
<td>Fungi (e.g. <em>Candida albicans</em>)¹</td>
<td>1-3%</td>
</tr>
<tr>
<td>Culture negative</td>
<td>10-20%</td>
</tr>
</tbody>
</table>

¹ Often after VAC-therapy or fistula (with antibiotic therapy).
Daptomycin activity against high-inoculum, stationary-phase MRSA in vitro

Time–kill assay of daptomycin against high-inoculum* MRSA (ATCC 43300) in stationary phase (mean ± SD, n=3)

*5 × 10^6 CFU/ml

OPAT in bone and joint infection

- Osteomyelitis & implant infections
  - Whenever possible => switch to oral (2 + 10 = 12 weeks)
  - Multiresistant organisms => difficult to treat (6 weeks)
  - Often no oral alternatives

- Possibilities for gram-positive cocci
  - Vancomycin (TDM, BID)
  - Teicoplanin (loading dose 800 mg OD, then 400 mg OD)
  - Daptomycin (high-dose: 10 mg/kg OD)
  - Investigational: lipoglycopeptides (oritavancin, telavancin)
Outline

- Biofilm and implants
- Diagnosis
  - Preoperative
  - Intraoperative
- Management
  - Surgical options
  - Antibiotics (local and systemic)
- Outlook
  - Controversies
67-y: Increasing pain after knee implantation 1 year ago. Which preoperative test most accurately detects infection?

a) Serum C-reactive protein (CRP)
b) Synovial fluid Gram stain & culture
c) Synovial fluid leukocyte count & differentiation
d) Conventional x-ray
e) PET / CT scan
An emeritus professor complains about hip pain, prosthesis is radiologically loose. During 1-stage exchange, a single tissue culture grew coagulase-negative staphylococcus. Which information helps to interpret this result?

a) CRP level  
b) Bacterial species & susceptibility  
c) Scintigraphy  
d) Date of arthroplasty  
e) Name of professor’s lawyer
Question No. 2

An emeritus professor complains about hip pain, prosthesis is radiologically loose. During 1-stage exchange, a single tissue culture grew coagulase-negative staphylococcus. Which information helps to interpret this result?

a) CRP level
b) Bacterial species & susceptibility
c) Scintigraphy
d) Date of arthroplasty: 12 years ago
e) Name of professor’s lawyer
ARTIFICIAL JOINT FAILURE:
loosening, dislocation, neurovascular deficits, tendon lesions, limb length discrepancy, poor range of motion, pain, sounds

- Acute or fatigue implant fracture, oxidative degradation, corrosion
- Artificial joint material failure
- Acute mechanical overload
- Chronic mechanical overload
- Bone to implant interface failure
- Effective joint space fluid pressure
- Implant positioning, poor approach
- Poor surgical technique
- Poor preoperative diagnosis
- Complication rate
- Poor education, low surgical volume

- Wear particles
  - MOP, MOM, COC bearing couples
- Infection
  - Osteolysis
    - Hypersensitivity, mutagenicity?
    - Metal ion release
- Excessive micromotion
  - Bone to implant toughness mismatch
- Periprosthetic fracture
  - Artifical joint material failure
- Sistemic alterations
  - Stress shielding, week bone
  - Unnatural force transfer
  - Excessive rigidity
- Excessive micromotion
- Bone to implant toughness mismatch

- Aggressive activity - sports
- Production errors, improper materials or design
- Effective joint space fluid pressure
Vitamin B$_{12}$ - Imaging

- Essencial growth factor
- Produced by 0.001% of living organisms, consumed by 99.999%:
  - Low uptake: Differentiated somatic cells
  - High uptake: Microorganisms, tumor cells
- Complex chemical structure (mammals & most bacteria unable to synthesize) → have efficient uptake systems

Can radiolabeled vitamin B$_{12}$ be used for imaging infections?
Vitamin B\textsubscript{12} for tumor diagnosis

\textsuperscript{In-111} Adenosylcobalamin 650 μCi (2.2 μg) i.v.

Accumulation in liver, spleen, salivary glands

Solution: Tumor-selective derivatives (not binding to transcobalamin II = TCII)

Calorimeter
Thermostat 37°C
$\Delta T < 10^{-6}° C$

Detection limit $\pm 20$ nW
$\approx 2000$ bacterial cells
Microcalorimetry of sonicate

![Graph showing heat flow over time for different bacterial species.](image)

S. aureus
S. epidermidis
S. pyogenes

Heat flow (μW)

Time (h)

0 4 8 12 16 20 24

Trampuz A et al. RMS 2010 (in press)
Basic questions

1. Do we want to diagnose PJI?
   - “If you don’t measure fever, you can’t have fever”

2. Do we believe that we can cure PJI?
   - “If you don’t believe, you will do everything to proof that another concept doesn’t work”

3. Do we have the courage to consider another concept?
   - “Or do we want to invent a wheel?”
Question No. 3

85-y-old biologist. Knee implantation 5 years ago, no complains until 2 weeks ago. Suddenly fever & joint swelling. Prosthesis is radiological stable. Which procedure would you suggest?

a) Joint puncture and antibiotic therapy
b) Arthroscopic lavage
c) Open revision with change of mobile parts
d) Prosthesis removal, reimplantation after 2 weeks
e) Leg amputation & new job search
Question No. 3

85-y-old biologist. Knee implantation 5 years ago, no complains until 2 weeks ago. Suddenly fever & joint swelling. Prosthesis is radiological stable. Which procedure would you suggest?

a) Joint puncture and antibiotic therapy
b) Arthroscopic lavage
c) Open revision with change of mobile parts
d) Prosthesis removal, reimplantation after 2 weeks
e) Leg amputation & new job search
65-y-old surgeon. Progressive hip pain since implantation 1 year ago. 1 month ago fistula occurred with growth of *S. epidermidis* in fistula swab. What would you suggest?

a) Ciprofloxacin + rifampicin p.o.
b) Debridement and retention
c) 1-stage exchange
d) 2-stage exchange: short interval (2 weeks)
e) 2-stage exchange: long interval (6-8 weeks)
Question No. 4

65-y-old surgeon. Progressive hip pain since implantation 1 year ago. 1 month ago fistula occurred with growth of *S. epidermidis* in fistula swab. What would you suggest?

a) Ciprofloxacin + rifampicin p.o.
b) Debridement and retention
c) 1-stage exchange
d) 2-stage exchange: short interval (2 weeks)
e) 2-stage exchange: long interval (6-8 weeks)
Quantitative assessment of DNA

Achermann Y et al. J Clin Microbiol 2010
"A man barely alive. We can rebuild him. We have the capability to build the world's first bionic man."

“???.”

7 million $
High-dose daptomycin for PJI: ongoing phase II study

- **Background:**
  - High-dose daptomycin is active against biofilm staphylococci
  - Rifampin can (in combination) eradicate staphylococcal biofilms
  - Long treatment for eradication of biofilms (3 months)

- **Inclusion criteria**
  - Type of prosthesis: Hip, knee, shoulder
  - Pathogen: Staphylococcus aureus or coagulase-negative staphylococci (susceptible to daptomycin, rifampin)
  - Other: 18-80 years old

- Non-comparative evaluation of daptomycin plus rifampin for PJI
  - Primary endpoint: cure rate
  - Secondary endpoint: safety
Osteoarticular infections

Prosthetic joint infection
- CNS, *S. aureus*
- *Streptococcus* spp.
- *Enterococcus* spp.
- *Propionibacterium acnes*

Vertebral osteomyelitis
- *S. aureus*
- Gramnegative bacilli
- *Streptococcus* spp,
- *Mycobacterium tuberculosis*

Septic arthritis
- *S. aureus*
- Streptococci
- Enterococci

Diabetic foot infection
- *S. aureus*
- *Streptococcus* spp.
- *Enterococcus* spp.
- Gramnegative bacilli
- Anaerobes

Post-traumatic infection
- *S. aureus*
- Polymicrobial
- Gramnegative bacilli

*S. aureus* is the most common causative pathogen of osteomyelitis
Disclosure note

Research grant received from Novartis Pharma

Conflict of interests

- Trained as ID specialist
- Thinking as a surgeon
- Practical approach taking decisions
Joint replacement

- One of the most successful intervention in modern medicine
- Improved quality of live in the increasingly elderly population
Primary joint replacement

Kurz et al. CORR 2009
Revision joint replacement:

- Aseptic failure
- Septic failure
Implants: improve function or replace missing anatomic structure.
86 explanted prostheses:

- 56 knee
- 25 hip
- 3 elbow
- 2 shoulder

Graph showing:
- Implant removal (%) over time after implantation (years)
- Prosthetic joint infection vs. aseptic failure
- Statistical analysis: p < 0.0001
- HR 4.6 [95% CI, 2.2-9.3]

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Time after implantation (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aseptic failure</td>
<td>62  28  14  8  4</td>
</tr>
<tr>
<td>Prosthetic joint infection</td>
<td>24  2  2  1  0</td>
</tr>
</tbody>
</table>
Dansk Hoftealloplastik Register

Year 2011 (n = 11,251)

www.dhr.dk
Biofilms and implants

**Microbial Biofilms: Sticking Together for Success**

Single-celled microbes readily form communities in resilient structures that provide advantages of multicellular organization.

**Waiting to grow**
Bacteria can shrink to a spore-like state to wait in water, soil—even rock or tissue—until conditions are right for active growth.

**Meeting the challenge**
While antimicrobials damage outer cell layers, the biofilm community can survive.

**Finding a niche**
Chemical gradients create micro-environments for different microbial species or levels of activity.

**Changing their spots**
Active bacteria will attach to virtually any surface. Within minutes, changes in gene expression transform "swimmers" to "stickers."

**Getting breakfast in bed**
Nutrients diffuse into the matrix as they flow by.

**Building houses of slime**
Attached bacteria multiply and encase their colonies with a slimy matrix.

**Going with the flow**
Propelled by shear forces, aggregated cells can break loose, roll, or ripple along a surface in sheets and remain in their protected biofilm state.

**Persisters**
Close proximity of cells facilitates the exchange of molecular signals that regulate behavior.

**Dispersers**
"Wall"
Orthopedic implants
## Diagnosis

### Preoperative

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Imaging</th>
<th>Synovial fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>L, ESR, CRP, PCT</td>
<td>X-ray, US</td>
<td>Leukocyte count</td>
</tr>
</tbody>
</table>

### Intraoperative

<table>
<thead>
<tr>
<th>Tissue specimens</th>
<th>New methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathology</td>
<td>Sonication</td>
</tr>
<tr>
<td>Gram / Culture</td>
<td>Bead beating</td>
</tr>
</tbody>
</table>

- **New methods:**
  - Sonication
  - Bead beating
  - PCR
  - Microcalorimetry
  - Mass spectrometry
Biomarkers in blood
Serum procalcitonin is a helpful diagnostic marker supporting clinical and microbiological findings for better differentiation of infectious from noninfectious causes of fever after orthopaedic surgery.

Hunziker S et al. JBJS-Am 2010
Prokaryote versus eukaryote cell

Prokaryote cell
- No independent organelles

Eukaryote cell
- Highly differentiated cells
Homo sapiens
(Latin: 'wise man')

Eukaryotic cells: $10^{13}$
Bacteria & fungi: $10^{14}$
Shark Bay, West-Australia: 2.5 billion years ago

**Cyanobacteria biofilms** allowed development of higher forms of life through $O_2$-production
Route of implant infection

Perioperative

- **Intraoperatively**: ≥100 bacteria sufficient
- **Postoperatively**: risk <48 hours

Hematogenous

Distant urinary, skin and respiratory infections
Diagnosis
Patient at lower probability of periprosthetic knee infection being assessed for infection

- ESR/CRP: either positive?
  - Yes: Aspirate joint
  - No: Continue

- Both Cell count/differential AND Culture positive?
  - Yes: Infection Likely
  - No: Continue

- Either cell count/differential OR culture positive?
  - Yes: Repeat aspiration: positive?
    - Yes: Frozen section AND/OR Intra-operative synovial fluid white blood cell count/differential: positive?
      - Yes: Infection Likely
      - No: Infection Unlikely
    - No: Observe and Re-evaluate at 3 months
  - No: Infection Unlikely

www.aaos.org/research
Painful prosthetic joint: Effusion => joint aspiration

Synovial fluid for:
- culture (native)
- leukocyte count (with anticoagulants, analysis within 24 h)

Inoculation in blood culture bottles improves sensitivity

Risk for iatrogenic infection under aseptic conditions extremely low (>0.01%)
Aspiration of prosthetic knee joints, underlying inflammatory disorders excluded.
Intraoperative tissue culture

Obtain ≥3 tissue specimens
  - No swabs, no sinus tract cultures!
  - Culture sensitivity: 60-80%
  - Prolonged culture incubation 7-14 d (anaerobes)

- Stop antibiotics 2 weeks before
- Delay surgical prophylaxis
Sonication for diagnosis of biofilm infections

Sonication
Mechanical vibrations >20 kHz

Microbubbles (cavitation)

www.bactosonic.info
Sonication of Removed Hip and Knee Prostheses for Diagnosis of Infection

Figure 2. Effect of Preoperative Antimicrobial Therapy on Culture Sensitivity in Patients with Prosthetic-Joint Infection.
Better sensitivity (80-90%)  
Quantitative (more specific)  
Mixed infections (30%)  
Faster, less expensive  
Fluid for additional investigations
Multiplex PCR (SeptiFast) in sonication fluid of PJI

Achermann Y et al. J Clin Microbiol 2010
## Multiplex PCR (SeptiFast) in sonication fluid of PJI and AF

<table>
<thead>
<tr>
<th>Type of diagnostic techniques</th>
<th>Prosthetic joint infection (n = 24)</th>
<th>Aseptic failure (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periprosthetic tissue culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 sample positive</td>
<td>2 (8%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7 (11%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥2 samples positive</td>
<td>17 (71%)</td>
<td>0</td>
</tr>
<tr>
<td>Sonication culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 CFU/ml</td>
<td>1 (4%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 (8%)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥50 CFU/ml</td>
<td>16 (67%)</td>
<td>1 (2%)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Multiplex-PCR of sonication fluid</td>
<td>23 (96%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Portillo ME et al. *J Clin Microbiol* 2012 (accepted)
Sonication studies with implants

- Shoulder prosthesis (Piper KE et al. JCM 2009)
- Breast implants (Del Pozo JL et al. JCM 2009)
- Breast implants (Rieger UM et al. Aesth Plast Surg 2009)
- Pacemakers and ICDs (Rohacek M et al. Circulation 2010)
- Spine implants (Sampedro M et al. Spine 2010)
- Ureteric catheters (Bonkat G et al. W J Urol 2010)
- Multiplex PCR in sonication fluid (Achermann Y et al. JCM 2010)
- Pacemakers (Mason PK et al. Pacing Clin Electrophysiol 2011)
- Joint prostheses (Sierra JM et al. Arch Orthop Trauma Surg 2011)
Therapy
Rififi: a 1955 French crime film

Adaptation of Auguste le Breton's novel.

The film earned Jules Dassin the award for Best Director at the 1955 Cannes Film Festival.

"I liked you Macaroni. But you know the rules"
ROLE OF RIFAMPIN IN IMPLANT-RELATED BONE INFECTIONS: A randomized controlled trial

**Treatment:** Initial débridement and antibiotics:

- **2 weeks i.v.**
  - Flucloxacillin or Vancomycin + Rifampin or Placebo

- followed by:

- **3-6 months p.o.**
  - Ciprofloxacin + Rifampin or Placebo

Zimmerli W et al. JAMA 1998
<table>
<thead>
<tr>
<th></th>
<th>Rifampin-placebo</th>
<th>Rifampin-combination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=15)</td>
<td>(n=18)</td>
</tr>
<tr>
<td>Microbiology:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- S. aureus</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>(0/26 methicillin-resistant)</td>
<td></td>
</tr>
<tr>
<td>- S. epidermidis</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>(2/7 methicillin-resistant)</td>
<td></td>
</tr>
<tr>
<td>Initial iv-treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Flucloxacillin</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>- Vancomycin</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>33 (15-41)</td>
<td>35 (24-46)</td>
</tr>
<tr>
<td>(median,range)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Zimmerli W et al. JAMA 1998
## Results

<table>
<thead>
<tr>
<th></th>
<th>CIP + placebo</th>
<th>CIP + RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure (ITT)</td>
<td>9/15 (60%)</td>
<td>16/18 (89%)</td>
</tr>
<tr>
<td>Cure (as treated)</td>
<td>7/12 (58%)</td>
<td>12/12 (100%)*</td>
</tr>
<tr>
<td>Drop-out</td>
<td>3/15</td>
<td>6/18</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>33 (15-41)</td>
<td>35 (24-46)</td>
</tr>
</tbody>
</table>

*p=0.019 (Fisher’s exact test)

Zimmerli W et al. JAMA 1998
Treatment outcome in 118 PJIs (1994–2006)*

- Debridement and retention: 75/81 (93%)
- One-stage exchange: 13/14 (93%)
- Two-stage exchange: 15/15 (100%)
- Prosthesis removal: 5/5 (100%)
- No surgery: 2/3 (67%)

*Infections included hip (n=78), knee (n=22), ankle (n=10) and shoulder (n=8)
Hip and knee PJI (n = 68)


- Adequate treatment
- Partially adequate treatment
- Inadequate treatment

Elbow PJI (n = 27)

According to algorithm
Probability of relapse-free survival

Not according to algorithm

Time after diagnosis of infection, years

Achermann Y et al. Clin Microbiol Infect 2010
Hip PJI (n = 63), 1985-2001

According to algorithm

Not according to algorithm

Giulieri S. Infection 2004
Débridement with retention of knee PJI

Debridement & Retention

No changing of mobile parts (n=14)

Changing of mobile parts (n=11)

1/14 (7%)

10/11 (91%)
Spacer and local antibiotics?

Temporary foreign body (spacer)

- Local elution of high antibiotic concentration
- Impregnated with antibiotics (vancomycin, gentamicin / tobramycin, clindamycin, daptomycin?)
- No rifampicin is needed in the interval before implantation (emergence of resistance)

Permanent fixation (cement)

- In revision knee surgery (vancomycin + gentamicin)
- Modified biomechanical properties
Science fiction: implant function better than native
Everything is perfect........
Definition & classification
Definition

- Sinus tract (fistula)
- Visible purulence\(^1\)
  - Wound discharge, abscess
- Acute inflammation in tissue histology
  - \(\geq 1\) to \(\geq 10\) neutrophils/high-power field
- Leukocytes in synovial fluid\(^2\)
  - Knee: \(\geq 1.7 \times 10^9/l\) leukocytes, \(\geq 65\%\) neutrophils
  - Hip: \(\geq 3.5 \times 10^9/l\) leukocytes, \(\geq 70\%\) neutrophils
- Microbial growth
  - Synovial fluid
  - \(\geq 3\) periprosthetic tissue (for low-virulent organisms \(>1\) positive)
  - Sonication fluid (>50 CFU/ml)

\(^1\) Pseudopus: metal-on-metal prostheses
\(^2\) Excluded: Early postoperative (3 months) and inflammatory joint diseases
<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Antimicrobial Agent</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> or coagulase-negative</td>
<td>Nafcillin or floxacillin* plus</td>
<td>2 g every 6 hr</td>
<td>IV</td>
</tr>
<tr>
<td><em>Staphylococcus</em> species (except <em>Streptococcus</em></td>
<td>Rifaximin for 2 wk, followed by</td>
<td>450 mg every 12 hr</td>
<td>PO or IV</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> or coagulase-negative</td>
<td>Rifaximin plus</td>
<td>450 mg every 12 hr</td>
<td>PO</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> or coagulase-negative</td>
<td>Ciprofloxacin or</td>
<td>750 mg every 12 hr</td>
<td>PO</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> or coagulase-negative</td>
<td>Levofloxacin</td>
<td>750 mg every 24 hr to 500 mg every 12 hr</td>
<td>PO</td>
</tr>
<tr>
<td>Methicillin-susceptible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>Vancomycin plus</td>
<td>1 g every 12 hr</td>
<td>IV</td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>Rifaximin for 2 wk, followed by</td>
<td>450 mg every 12 hr</td>
<td>PO or IV</td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>Rifaximin plus</td>
<td>450 mg every 12 hr</td>
<td>PO</td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>Ciprofloxacin or</td>
<td>750 mg every 12 hr</td>
<td>PO</td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>Levofloxacin</td>
<td>750 mg every 24 hr to 500 mg every 12 hr</td>
<td>PO</td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>Teicoplanin or</td>
<td>400 mg every 24 hr</td>
<td>IV or IM</td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>Fusidic acid or</td>
<td>500 mg every 8 hr</td>
<td>PO</td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>Trimethoprim---sulfamethoxazole or</td>
<td>1 DS tablet every 8 hr</td>
<td>PO</td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>Minocycline</td>
<td>100 mg every 12 hr</td>
<td>PO</td>
</tr>
<tr>
<td>Streptococcus species (except <em>Streptococcus</em></td>
<td>Penicillin G or</td>
<td>5 million U every 6 hr</td>
<td>IV</td>
</tr>
<tr>
<td><em>agalactiae</em>)</td>
<td>Ceftriaxone for 4 wk, followed by</td>
<td>2 g every 24 hr</td>
<td>IV</td>
</tr>
<tr>
<td>Streptococcus species (except <em>Streptococcus</em></td>
<td>Amoxicillin</td>
<td>750–1000 mg every 8 hr</td>
<td>PO</td>
</tr>
<tr>
<td><em>agalactiae</em>)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus species (penicillin-susceptible)</td>
<td>Penicillin G or</td>
<td>5 million U every 6 hr</td>
<td>IV</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em> and <em>Enterococcus</em></td>
<td>Ampicillin or amoxicillin plus</td>
<td>2 g every 4–6 hr</td>
<td>IV</td>
</tr>
<tr>
<td><em>Enterococcus species</em> (penicillin-susceptible)</td>
<td>Aminoglycoside* for 2–4 wk,</td>
<td></td>
<td>IV</td>
</tr>
<tr>
<td><em>and Streptococcus agalactiae</em></td>
<td>followed by</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus species</em> (penicillin-susceptible)</td>
<td>Amoxicillin</td>
<td>750–1000 mg every 8 hr</td>
<td>PO</td>
</tr>
</tbody>
</table>