Treatment of PJI

Andrej Trampuz
Charité – University Medicine Berlin
Germany
Implants improved life quality
Treatment
Treatment concept

To achieve high treatment success, a concerted surgical and antimicrobial concept is needed

Cure rate >90%
**Treatment algorithm**

**Acute PJI**
- Good bone/soft tissue?
- Stable prosthesis?
- No DTT (if known).Must be filled 

Yes → Débridement & retention, exchange of mobile parts

No → Prosthesis exchange

**Chronic PJI**
- DTT (if known)?
- Bad bone/soft tissue?
- Fistula?
- Multiple revisions?

Yes → Eradication of infection not possible

No → Prosthesis exchange

- DTT (if known)?
- Bad bone/soft tissue?
- Fistula?
- Multiple revisions?

Yes → Three-stage exchange

No → One-stage exchange

**Two-stage exchange**
- DTT-organism?
- Bad bone/soft tissue?

Yes → Long interval (6-8 weeks)

No → Short interval (2-3 weeks)

**Three-stage exchange**

DTT = difficult-to-treat infections caused by pathogens resistant to biofilm-active antimicrobials
- Rifampin-resistant staphylococci
- Ciprofloxacin-resistant gram-negative bacteria
- Fungi (Candida)
Acute infection
Prolonged discharge: early postoperative PJI?

- C-reactive protein (CRP) should decrease after surgery!
- Exclude other reasons of prolonged discharge (coagulopathy, hematoma, albumin deficiency)

→ revision surgery if prolonged discharge (>7-10 days)
Acute pain & fever, 10 y after implantation
The solution to pollution is dilution

Systemic antibiotic

Bacterial count (log)

No surgery

Insufficient debridement, Sufficient debridement, change of mobile parts

Resistant strains

Time

Always surgery
Antibiotics without surgery

Cure rate 8%

Cure rate 9%

Always (!): Change of mobile parts

Acute hip and knee infection

Debridement & retention

Intervention

Not changing mobile parts
4/52 (7%)

Changing of mobile parts
50/55 (91%)

Clinical success
CURRENT CONCEPTS

Prosthetic-Joint Infections

Werner Zimmerli, M.D., Andrej Trampuz, M.D., and Peter E. Ochsner, M.D.

CURRENT CONCEPTS

Prosthetic-Joint Infections

Werner Zimmerli, M.D., Andrej Trampuz, M.D., and Peter E. Ochsner, M.D.
Chronic infection
• 78-y-o female
• Primary hip prosthesis 4 months ago
• Since implantation pain, walking distance now 20 m
• CRP normal, no loosening on x-ray
Aspiration 4 months after implantation

**High leukocyte count in joint aspirate (59,000/µl)**

### Mikroskopische Untersuchungen

<table>
<thead>
<tr>
<th>Grampräparat</th>
<th>Leukozyten</th>
<th>Mikroorganismen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mässig</td>
<td>nicht nachweisbar</td>
</tr>
</tbody>
</table>

### Kulturelle Ergebnisse

1. **Staphylococcus epidermidis** nach Anreicherung

<table>
<thead>
<tr>
<th>Antibiotikum</th>
<th>Ergebnis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>R</td>
</tr>
<tr>
<td>Amoxicillin + Clavulansäure</td>
<td>R</td>
</tr>
<tr>
<td>Cefalotin</td>
<td>R</td>
</tr>
<tr>
<td>Ceftriaxon</td>
<td>R</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>R</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>R</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>R</td>
</tr>
<tr>
<td>Cotrimoxazol</td>
<td>R</td>
</tr>
</tbody>
</table>

- **Tetrazyklin** S
- **Imipenem** R
- **Penicillin** R
- **Oxacillin** R
- **Clindamycin** R
- **Erythromycin** S
- **Rifampicin** S
- **Vancomycin** S
- **Fusidinsäure** R

S = sensibel  
I = intermediär  
R = resistent  
f = folgt  
N = negativ  
P = positiv

Validiert durch: Irene Grohsellus
Delayed (low-grade) infection

**Joint aspiration:**
- Culture: *Staphylococcus epidermidis*
- Cell count: 59,000/µl leukocytes, 90% PMN
- CRP normal, no prosthesis loosening

**Prosthesis exchange:**
- 1-stage exchange OR
- 2-stage exchange with short interval (2 weeks)
Treatment algorithm: chronic infection

Chronic PJI

Prosthesis exchange

- DTT (if known)?
- Bad bone/soft tissue?
- Fistula?
- Multiple revisions?

One-stage exchange

Two-stage exchange

- DTT-organism?
- Bad bone/soft tissue?

Three-stage exchange

- DTT-organism?
- Bad bone/soft tissue?

Yes

No

Short interval (2-3 weeks)

Long interval (6-8 weeks)

Unsatisfactory course?

DTT = difficult-to-treat infections caused by pathogens resistant to biofilm-active antimicrobials
- Rifampin-resistant staphylococci
- Ciprofloxacin-resistant gram-negative bacteria
- Fungi (Candida)
Aim of PJI-algorithm

To select the

• **least invasive** treatment option depending on the present features
• with the **best functional result**
• without compromising the cure rate!
Surgical procedures

**Type of surgery**

- Retention of fixed prosthetic components
- One-stage exchange
- Two-stage exchange (short interval)
- Two-stage exchange (long interval)
- Three-stage exchange

**Intervention**

- Change of mobile parts
- Explantation & implantation

**Antibiotics (total 12 weeks)**

- 2 weeks
- 10 weeks
- 2 weeks
- 1 week
- 9 weeks
- 2 weeks
- 4 weeks
- 1 week
- 5 weeks
- 3 weeks
- 3 weeks
- 1 week
- 5 weeks

**Intervention details**

- Débridement & biopsies
- i.v. antibiotics
  - **without** antibiofilm activity
- p.o. antibiotics
  - **without** antibiofilm activity
- p.o. antibiotics **with** antibiofilm activity
- Ex- and reimplantation of prosthesis

**Biofilm treatment**
### Surgical procedures

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Intervention</th>
<th>Antibiotics (total 12 weeks)</th>
</tr>
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<tbody>
<tr>
<td>Retention of fixed</td>
<td></td>
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<tr>
<td>prosthetic components</td>
<td></td>
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</tr>
<tr>
<td>One-stage exchange</td>
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<tr>
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<tr>
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<td></td>
</tr>
<tr>
<td>Three-stage exchange</td>
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- **Retention of fixed prosthetic components**
  - Change of mobile parts: 2 weeks, 10 weeks
  - Explantation & implantation

- **One-stage exchange**
  - Explantation & implantation: 2 weeks, 10 weeks

- **Two-stage exchange (short interval)**
  - Explantation, Implantation: 2 weeks, 1 week, 9 weeks

- **Two-stage exchange (long interval)**
  - Explantation, Implantation: 2 weeks, 4 weeks, 1 week, 5 weeks

- **Three-stage exchange**
  - Explantation, Implantation: 3 weeks, 1 week, 5 weeks

**Antibiotics**
- i.v.
  - Without antibiofilm activity
- p.o.
  - Without antibiofilm activity
  - With antibiofilm activity

**Surgical procedures**
- Débridement & biopsies
- Osteomyelitis treatment
- Ex- and reimplantation of prosthesis
Strategy: long interval (6 weeks)

- **No prosthesis**
  - Osteomyelitis therapy
    - Suppression

- **Prosthesis**
  - Biofilm-active therapy
    - Eradication

**No rifampin during interval!**

**rifampin**
No drug holidays before reimplantation

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<tr>
<td>Three-stage exchange</td>
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- **Change of mobile parts**: 2 weeks, 10 weeks
- **Explantation & implantation**
  - One-stage exchange (short interval): 2 weeks, 1 week, 9 weeks
  - Two-stage exchange (long interval): 2 weeks, 4 weeks, 1 week, 5 weeks
  - Three-stage exchange: 3 weeks, 3 weeks, 1 week, 5 weeks

- Débridement & biopsies
  - i.v. antibiotics
  - p.o. antibiotics with antibiofilm activity

- p.o. antibiotics without antibiofilm activity

- Ex- and reimplantation of prosthesis

- **Antibiotics (total 12 weeks)**
“Fast-track”-study: Short vs. long interval in two-stage prosthesis exchange

**First Stage (Short Interval):**
- Explantation: 3 weeks i.v.
- Implantation: 4 weeks i.v.

**Second Stage (Long Interval):**
- Explantation: 7 weeks
- Implantation: 4 weeks p.o. 1 week i.v. 4 weeks p.o.
Interval from explantation until reimplantation (hip & knee PJI)

Cure rate >90%

**Year**


**Median (days)**

95 99 105 90 110 80 71 75 66 43 32 21 19
Acute infections (<3 weeks of symptoms)
- Stable prosthesis
- Good soft tissue
- No difficult to treat organism (see below)

Yes

Difficult-to-treat organism?
- Rifampin-R staphylococcus
- Ciprofloxacin-R Gram- rods
- Fungi

No

Yes

Debridement and retention
2 weeks i.v.
10 weeks p.o.

Debridement

One stage

Explantation and implantation
2 weeks i.v.

“Biofilm treatment” (with rifampin if applicable)

Only if good soft tissue

Two stage (short interval)

Explantation
Implantation
2-3 weeks i.v.

“Osteomyelitis treatment” (no rifampin)

Two stage (long interval)

Explantation
Implantation
6 weeks i.v.
2 weeks i.v.

No treatment

Explantation
Implantation

“Osteomyelitis treatment” (no rifampin)
2 stage exchange: removal of all foreign material
No drug holidays

- No need: does not change the further treatment
- Not sensitive (local antibiotics if spacer in situ)
- Misleading (if false positive/contamination)
- Additional intervention - additional risk of infection
- Prolonged treatment (longer exposure to antibiotics and spacer, longer period of immobility)
- Holidays for patient = holidays for bacteria → implantation of a new prosthesis when bacteria are recovered
Antibiotics
Properties of antibiotics

Bactericidal activity

Good oral bioavailability

Good bone penetration

Activity against biofilms
Bactericidal activity

How much ends up in the bone?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral bioavailability</th>
<th>Bone penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin/Sulbactam</td>
<td>50%</td>
<td>7%</td>
</tr>
<tr>
<td>Cefuroxim, cefadroxil</td>
<td>50%</td>
<td>12%</td>
</tr>
<tr>
<td>Levofloxacine</td>
<td>100%</td>
<td>77%</td>
</tr>
<tr>
<td>Rifampin</td>
<td>80%</td>
<td>51%</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>85%</td>
<td>55%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>90%</td>
<td>45%</td>
</tr>
<tr>
<td>Linezolid</td>
<td>100%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Sanford Guide to Antimicrobial Therapy 2015. 45nd ed.
Lorian. Antibiotics in Laboratory Medicine. 5th ed.
Antibiotics with biofilm-activity

- **Staphylococci**: rifampin (in combination)
- **Gram-negative rods**: ciprofloxacin
- **Streptococci**: penicillin G (amoxicillin p.o.)
- **Enterococci**: ampicillin + gentamicin
Foreign body infection (FBI) model in guinea pigs

- Subcutaneous implantation of 4 Teflon “cages”
- Infection of cages with different inocula
- Systemic treatment of infection
- Aspiration of cage-fluid (planctonic bacteria?)
- Removal of cages after 5 days and sonication of cages

Staphylococcal PJI

El Helou et al. EJCMID 2010
Targeted therapy
Empiric treatment

No specific exposure:
→ Ampicillin/Sulbactam

Fistula, VAC, multiple revisions etc:
→ Piperacillin/Tazobactam

Several previous interventions, MRSA-carrier:
→ normal renal function (eGFR > 60ml/min): add Vancomycin
Switch to oral treatment after surgery

When...
... CRP is nearly normalized
... wound is closed and dry
... organism and its susceptibility is known

→ usually after 2 weeks
Rifampin – precious but delicate
Rifampin

- Check **interactions** (CYP450-induction; anticoagulants, antiepileptics, antihypertensive agents, immunomodulators etc)
- Monitor **liver enzymes** (toxic hepatitis)
- Inform patient about red coloration of body fluids (urine, tears)
Rifampin: Quick emergence of resistance

Do not use:

• Before surgery
• In the interval before re-implantation of prosthesis
• In open wounds
• As single antibiotic (monotherapy)
Therapy during interval: suppression

➢ Aim: suppression of the infection (no eradication)

➢ used substances:

<table>
<thead>
<tr>
<th>Organism</th>
<th>substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococci</td>
<td>Cotrimoxazol, Doxycyclin, Clindamycin</td>
</tr>
<tr>
<td>Streptococci</td>
<td>Amoxicillin, Clindamycin, Levofloxacin</td>
</tr>
<tr>
<td>Enterococci</td>
<td>Amoxicillin, (Linezolid)</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>Clindamycin, Amoxicillin, Metronidazole</td>
</tr>
<tr>
<td>Gram negative organisms</td>
<td>Ciprofloxacin, Cotrimoxazol</td>
</tr>
</tbody>
</table>

➢ Seamless intake until implantation (no drug holidays)
Suppression with antibiotic cycling

• Longterm antibiotic therapy is splitted in treatment phases with different antibiotics instead of a single drug

• Changement of substance every 2-4 weeks

• Indications:
  – No anti-biofilm-active agent available
  – Intolerance of antibiotics/side effects

• Benefits:
  – Bacteria are getting confused → prevention of emergence of resistance
  – Antibiotic tolerance is better, adverse effects are less

4 weeks cotrimoxazol
4 weeks drug holidays
4 weeks doxycyclin
4 weeks clindamycin
Warum Fosfomycin?
Anforderung an ein Antibiotikum zur Therapie von Periprothetischen Infektionen (PPI)

✓ adäquate Penetration in Haut/Weichteil, Knochen und Biofilm

Konzentrationsprofil nach Gabe von 100 mg/kg Fosfomycin

Nach 3 h Knochenspiegel = Serum-/Weichgewebspiegel

Fosfomycin
Vancomycin

Schintler 2009
Prosthetic Joint Infection Outcome with Fosfomycin
The PROOF-study

Andrej Trampuz, MD • Head of Septic Surgery Unit • Center for Musculoskeletal Surgery • Charité – University Medicine Berlin
Allergy

Drug fever

Toxic hepatitis

Toxic nephritis

Electrolyte imbalance

Adverse effects

Psychologic disturbances

Myelosuppression

Diarrhea

C. difficile infection

Eosinophilic pneumonia

Achilles tendinopathy
Monitoring und dose adjustment

**Monitoring**

Through level: **Vancomycin**
- 2x/week

**Blood count, creatinin, electrolytes** 1x/week

**Liver enzymes** (Rifampin)
- every 2-4 weeks

**Dose adjustment**

Kidney function (eGFR 50ml/min)
- **Age**: reduce dose in patients >75 Jahre

- **Weight**: (>100kg and <40kg)
Pathogenesis
Pathogenesis of PJI

- **Hematogenous spread** from a distant focus through blood: 20%
- **Contiguous spread** from adjacent infected tissue: 5%
- **Peri-/post-interventional colonisation**: 75%

PJIs treated at Charité, 01/2017-01/2018
## Diagnostic tests

<table>
<thead>
<tr>
<th>Positive test</th>
<th>All episodes (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased serum CRP (&gt;10 mg/l)</td>
<td>96/104 (92)</td>
</tr>
<tr>
<td>Pathological WBC (&gt;10 G/l or &lt;4G/l)</td>
<td>61/104 (59)</td>
</tr>
<tr>
<td>Elevated synovial fluid leukocyte count</td>
<td>64/64 (100)</td>
</tr>
<tr>
<td>Peri-implant tissue histopathology</td>
<td>86/95 (91)</td>
</tr>
<tr>
<td>Culture (synovial fluid, tissue or sonication fluid)</td>
<td>99/106 (93)</td>
</tr>
<tr>
<td>Blood culture</td>
<td>43/70 (61)</td>
</tr>
</tbody>
</table>

→ PJI is easy to diagnose

Rakow A, Renz N (own data)
Pathogens

- Highly virulent, i.e. *S. aureus*, gram-negative bacilli, *Streptococcus* spp.
  

- Predominantly **monobacterial** infections

  - 104 monobacterial
  - 1 polymicrobial
  - 1 culture-negative

  Rakow A, Renz N (own data)
Primary foci: cohort of 106 episodes

- 1 (+3?) colon adenoma
- 1 GI bleeding
- 2 GI infections
- 7 dental treatments
- 5 dental infections
- 2 manipulations
- 10 infections
- 9 skin erosion (pedicure, skin disease, chronic ulcers)
- 7 skin and soft tissue infections
- 14 endocarditis
- 5 infected CIED
- 3 catheter infections

Rakow A, Renz N (own data)
# Investigation of cause

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Source</th>
<th>Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococci</strong></td>
<td></td>
<td>Blood cultures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Echocardiography (TEE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin examination</td>
</tr>
<tr>
<td><strong>Streptococci</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• S. oralis/mitis</td>
<td></td>
<td>Orthopantomogram (OPTG), dentist, TEE</td>
</tr>
<tr>
<td>• S. agalactiae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• S. dysgalactiae</td>
<td></td>
<td>Urinanalysis, imaging abdomen, skin examination, OPTG</td>
</tr>
<tr>
<td>• S. bovis/gallolyticus</td>
<td></td>
<td>Colonoscopy</td>
</tr>
<tr>
<td><strong>Enterococci</strong></td>
<td></td>
<td>Urinanalysis, TEE</td>
</tr>
<tr>
<td><strong>Enterobacteriaceae</strong></td>
<td></td>
<td>Urinanalysis, CT Abdomen</td>
</tr>
</tbody>
</table>

Renz N., Chirurg, 2017
Reality

- Studies not usable (wrong design)
- Significant bacteremia after dental interventions
- Prophylaxis reduces bacteremia
- Clinical practice: association exists
- Prospective studies needed

Bacteremia after tooth brushing and dental extraction

Lockhart PB. Circulation. 2008
Workshop on Prosthetic Joint Infection (PJI)

Berlin, Germany

April 9–10, 2018
June 25–26, 2018
September 27–28, 2018
December 13–14, 2018

Scientific Coordinators:
Dr. Andrej Trampuz and Dr. Nora Renz
Charité – Universitätsmedizin, Berlin, Germany

The goal: Advancing knowledge

To review, update and advance theoretical and practical knowledge in diagnosis, treatment and prevention of implant-associated infections. At the end of the workshop, participants should be able to generate a rational and efficient management plan in an interdisciplinary team.

The challenge: Biofilm and implants

Implant-associated infections occur in 1-5% after primary and up to 20–30% after revision surgery. Bacteria grow on medical devices as biofilm, making them difficult to detect and to eradicate. These infections cause considerable morbidity and increase healthcare costs. An efficient concept can significantly improve the treatment outcome and life quality of patients.

The solution: Teamwork

The key to success is an interdisciplinary approach integrating the latest evidence, clinical experience and innovations in diagnosis, local and systemic antimicrobials and surgical techniques.
CONSULTATION SERVICE ON IMPLANT INFECTIONS

The Consultation Service of the PRO-IMPLANT Foundation provides advice to healthcare professionals on the management of complex bone, joint and implant-associated infections.

CONSULTATION SERVICE
Website: cs.pro-implant-foundation.org

CONSULTATION SERVICE PORTAL
cs.pro-implant-foundation.org

FREE
Consultation service: www.pro-implant-foundation.org

THE CONSULTATION SERVICE IS PROVIDED BY AN INTERDISCIPLINARY TEAM:

- INFECTIOUS DISEASES SPECIALISTS
- ORTHOPEDIC AND TRAUMA SURGEONS
- MICROBIOLOGISTS AND PHARMACISTS

We provide practical advice on diagnosis, prevention and treatment of implant-associated infections, based on current knowledge and scientific evidence.

AVAILABILITY AND PRICE:
During the test period, the consultation service is free of charge. Further information is available at cs.pro-implant-foundation.org.

LEGAL DISCLAIMER:
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Focus on implant, bone and joint-associated infections:
• Surgery: New concepts (retention, 1-stage, 2-stage short interval)
• Diagnosis: Fast innovative methods
• Antibiotics: Active against biofilms
Thank you!

andrej.trampuz@charite.de

www.pro-implant-foundation.org