Management of vascular prosthesis infection: Current standards and future challenges

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Charité – University Medicine
Berlin, Germany
Implants improved the quality of life
Science fiction: implant function better than native
Infection remains one of the most challenging complication after surgery.
## 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* 2011;33:1567–1572
Key to success: interdisciplinary concept

- Diagnosis
- Antibiotics (Directed against biofilms)
- Surgery

Cure rate: 80-90%
Infection is a manageable complication, if…

…appropriate diagnostic is combined with
…correct surgery and
…efficient anti-biofilm agents.

Much room for improving the outcome and prevent infections.
Modern concepts
Diagnosis and Treatment of Prosthetic Joint Infection

Definition

Diagnosis of periprosthetic joint infection is confirmed if at least 1 criteria is fulfilled:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical features</td>
<td>20-30%</td>
<td>100%</td>
</tr>
<tr>
<td>Histology</td>
<td>95-100%</td>
<td>95-99%</td>
</tr>
<tr>
<td>Cytology</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>Microbiology</td>
<td>80-85%</td>
<td>97%</td>
</tr>
</tbody>
</table>

Clinical features:
- Staphylococcus (nodule) or visible
- Periprosthetic infection

Histology:
- Acute inflammation in periprosthetic tissue (>10 neutrophils per HPF)

Cytology:
- > 2000/pL leukocytes or
- > 70% granulocytes

Microbiology:
- Synovial fluid
- Periprosthetic tissue samples
- S. aureus or S. epidermidis

Note: S. aureus is sensitive to antibiotics (e.g., methicillin and vancomycin), while S. epidermidis is resistant.
Biofilm
Evolution of life on Earth

- 4.6 billion years ago: Development of Earth
- 3.5 billion: First life forms
- 2.5 billion: Cyanobacteria form biofilms
Normal flora of the skin and mucosa

*Homo sapiens*
(Latin: 'wise man')

- Eukaryote cells: $10^{13}$
- Microorganisms: $10^{14}$
- Bacteriophages: $10^{16}$
Taxonomy of microorganisms

Bacterial meningitis
- Streptococcus pneumoniae
- Neisseria meningitidis
- Haemophilus influenzae
- Streptococcus agalactiae
- Listeria monocytogenes

Sinusitis
- Streptococcus pneumoniae
- Haemophilus influenzae

Otitis media
- Streptococcus pneumoniae

Pneumonia
Community-acquired:
- Streptococcus pneumoniae
- Haemophilus influenzae
- Staphylococcus aureus
Atypical:
- Mycoplasma pneumoniae
- Chlamydia pneumoniae
- Legionella pneumophila

Tuberculosis
- Mycobacterium tuberculosis

Gastritis
- Helicobacter pylori

Food poisoning
- Campylobacter jejuni
- Salmonella
- Shigella
- Clostridium
- Staphylococcus aureus
- Escherichia coli

Sexually transmitted diseases
- Chlamydia trachomatis
- Neisseria gonorrhoeae
- Treponema pallidum
- Ureaplasma urealyticum
- Haemophilus ducreyi

Eye infections
- Staphylococcus aureus
- Neisseria gonorrhoeae
- Chlamydia trachomatis

Upper respiratory tract infection
- Streptococcus pyogenes
- Haemophilus influenzae

Urinary tract infections
- Escherichia coli
- Other Enterobacteriaceae
- Staphylococcus saprophyticus
- Pseudomonas aeruginosa

Skin infections
- Staphylococcus aureus
- Streptococcus pyogenes
- Pseudomonas aeruginosa
Planktonic bacteria & granulocytes
Biofilm

- Adherent to surface (min-h)
- Embedded in matrix (70%)
- Slowly replicating (stationary phase)
Complex interaction

- **Antibiotics**
  - Antimicrobial resistance

- **Microorganism**
  - (biofilm formation, susceptibility)

- **Virulence**

- **Host**
  - (inflammatory response)

- **Defense**

- **Implant**

- **Adherence**

- **Biocompatibility**
Experimental foreign-body infection (S. aureus)

3 h after inoculation

⇒ Rapid adherence, no elimination by granulocytes.

24 h after inoculation

Zimmerli et al. J Infect Dis 1982
The „fatal“ attraction

- **Foreign body** = avascular tissue (local immune defect): frustrated phagocytosis
- **Low number** of bacteria ($\approx 200$) sufficient to cause biofilm on implant
- **Mature biofilm** (>3 weeks) impossible to eradicate without implantremoval
Killing depends on age of the biofilm (in vitro)

The older the biofilm, the lower the bacterial killing

Antimicrobial tolerance in biofilms. In: Microbiol Spectr 3: June 2015
Acute local & systemic signs (fever)
Is it an infection? Deny the problem

Ostriches
... bury their heads in the sand to avoid danger

Humans
... avoid an apparently risky situation by pretending it doesn’t exist

The ostrich effect
Classification: early – delayed – late

<table>
<thead>
<tr>
<th>Time after implantation</th>
<th>&lt;1 month</th>
<th>3–36 months</th>
<th>Any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of infection</td>
<td>Early</td>
<td>Delayed</td>
<td>Late</td>
</tr>
<tr>
<td></td>
<td>postoperative</td>
<td>(low grade)</td>
<td></td>
</tr>
<tr>
<td>Route</td>
<td>Perioperative</td>
<td>Haematogenous</td>
<td></td>
</tr>
<tr>
<td>Signs</td>
<td>Acute: fever, effusion, warmth, dehiscence</td>
<td>Chronic: anastomosis leakage, bacteremia</td>
<td>Acute or subacute</td>
</tr>
<tr>
<td>Pathogen</td>
<td>S. aureus Streptococci Enterococci Gram-negative</td>
<td>Staph. epidermidis Cutibacterium acnes anaeorbes</td>
<td>S. aureus Streptococci Enterococci Gram-negative</td>
</tr>
</tbody>
</table>
Diagnosis
Normal skin flora

100,000 bacteria/cm²

- **Staphylococci**
  - *Staphylococcus epidermidis*
  - *Staphylococcus aureus*

- **Anaerobes**
  - *Cutibacterium acnes*
# Microbiology of PJI

<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>30-43%</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>12-23%</td>
</tr>
<tr>
<td>Streptococci &amp; enterococci</td>
<td>12-19%</td>
</tr>
<tr>
<td>Gram-negative bacilli (e.g. <em>Escherichia coli</em>)</td>
<td>10-17%</td>
</tr>
<tr>
<td>Anaerobes (e.g. <em>Cutibacterium acnes</em>)</td>
<td>4-10%</td>
</tr>
<tr>
<td>Mixed infections&lt;sup&gt;1&lt;/sup&gt;</td>
<td>10-20%</td>
</tr>
<tr>
<td>Fungi (e.g. <em>Candida albicans</em>)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1-3%</td>
</tr>
<tr>
<td>Culture negative</td>
<td>10-30%</td>
</tr>
</tbody>
</table>

<sup>1</sup> Often after VAC-therapy or fistula (with antibiotic therapy)

Corvec IJAO 2012; Tande CMR 2014

Low virulent organisms
Intraoperative tissue culture

Obtain ≥3 tissue specimens
- Interface tissue-prosthesis, no swabs
- For culture and histology
- Prolonged culture incubation: 10-14 d (anaerobes)
- Culture sensitivity: 60-80%

Schäfer P. Clin Infect Dis 2008
Sonication of implants

Sonication of Removed Hip and Knee Prostheses for Diagnosis of Infection

Sonication – biofilm bacteria
Sonication – biofilm bacteria

Sonication fluid

Tissue biopsy

Better sensitivity (80-90%)
Quantitative (more specific)
Mixed infections (30%)
Faster, less expensive
Fluid for additional investigations

Sonication fluid
Sonication studies with implants

- Shoulder prosthesis (Piper KE et al. JCM 2009)
- Breast implants (Rieger UM et al. Aesth Plast Surg 2009)
- Electrophysiologic cardiac devices (Rohacek M et al. Circulation 2010)
- Spine implants (Sampedro M et al. Spine 2010)
- Ureteric catheters (Bonkat G et al. W J Urol 2010)
- Pacemaker (Mason PK et al. Pacing Clin Electrophysiol 2011)
- Osteosynthesis material (Portillo ME et al. J Clin Microbiol 2015)
- External ventricular drains (Walti L et al. J Infect 2013)
Alpha defensin

- **Alpha defensin** is an antimicrobial peptide released by neutrophils

- Previous studies showed **high accuracy** of quantitative determination of alpha defensin (ELISA) for discrimination between aseptic failure (AF) and periprosthetic joint infection (PJI)

- **Qualitative** bed side lateral flow test is based on alpha defensin concentration in synovial fluid for detection of PJI

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative alpha defensin (ELISA)</td>
<td>97-100%</td>
<td>95-100%</td>
<td>Bingham J, CORR 2014&lt;br&gt;Deirmengian C, CORR 2014 and 2015&lt;br&gt;Frangiamore SJ, J Arthroplasty 2016&lt;br&gt;Wyatt MC, JBJS 2016&lt;br&gt;Bonanzinga T, CORR 2017</td>
</tr>
</tbody>
</table>
Lactic acid

**L-lactate** is constantly produced during metabolism and exercise

D-Lactate production in mammals is extremely low, with normal serum concentrations in the nano to micromolar range \((\text{nMol} - \text{µMol})\).

**D-lactate** is produced by bacteria as a product of bacterial fermentation

D-lactate concentration is increased to millimolar range \((\text{mMol})\) in bacterial infection.

*L. Szalay 2003; Sh.M. Smith 994*

*Wellmer A. 2001; Gratacós J. 1995*
D-Lactate in fluid of implants

Analysis of 148 implants
- 44 infections, 104 aseptic failures

Sensitivity 86%
Specificity 82%

50 μl of fluid
45 minutes

Yermak K, 2018 in press
Treatment
Treatment concept

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

Cure rate >90%
CURRENT CONCEPTS

Prosthetic-Joint Infections

Werner Zimmerli, M.D., Andrej Trampuz, M.D., and Peter E. Ochsner, M.D.
The solution to pollution is dilution

Bacterial count (log)

Systemic antibiotic

Resistant strains

No surgery

Insufficient debridement,

Sufficient debridement, change of mobile parts

Time

Always surgery
Treatment algorithm

**Acute PJI**
- Good bone/soft tissue?
- Stable prosthesis?
- No DTT (if known)_YES?

- Débridement & retention, exchange of mobile parts

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

- One-stage exchange
- No

**Long-term suppressive antibiotic therapy, permanent arthrodesis/girdlestone**

**Eradication of infection not possible**

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

- Yes

- Three-stage exchange

**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

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Intervention</th>
<th>Antibiotics (total 12 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention of implant</td>
<td>Debridement</td>
<td>2 weeks 10 weeks</td>
</tr>
<tr>
<td>One-stage exchange</td>
<td>Explantation &amp; implantation</td>
<td>2 weeks 10 weeks</td>
</tr>
<tr>
<td>Two-stage exchange (short interval)</td>
<td>Explantation  Implantation</td>
<td>2 weeks 1 week 9 weeks</td>
</tr>
<tr>
<td>Two-stage exchange (long interval)</td>
<td>Explantation  Implantation</td>
<td>2 weeks 4 weeks 1 week 5 weeks</td>
</tr>
<tr>
<td>Three-stage exchange</td>
<td>Explantation  Implantation</td>
<td>3 weeks 3 weeks 1 week 5 weeks</td>
</tr>
</tbody>
</table>

- 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>
</thead>
<tbody>
<tr>
<td>Retention of fixed prosthetic components</td>
<td>Change of mobile parts</td>
<td>2 weeks</td>
</tr>
<tr>
<td></td>
<td>Explantation &amp; implantation</td>
<td>2 weeks</td>
</tr>
<tr>
<td>One-stage exchange</td>
<td>Explantation</td>
<td>2 weeks</td>
</tr>
<tr>
<td></td>
<td>Implantation</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Two-stage exchange (short interval)</td>
<td>Explantation</td>
<td>2 weeks</td>
</tr>
<tr>
<td></td>
<td>Implantation</td>
<td>1 week</td>
</tr>
<tr>
<td>Two-stage exchange (long interval)</td>
<td>Explantation</td>
<td>3 weeks</td>
</tr>
<tr>
<td></td>
<td>Implantation</td>
<td>1 week</td>
</tr>
<tr>
<td>Three-stage exchange</td>
<td>Explantation</td>
<td>3 weeks</td>
</tr>
<tr>
<td></td>
<td>Implantation</td>
<td>1 week</td>
</tr>
</tbody>
</table>

Explantation & implantation

- 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

Soft tissue treatment
Properties of antibiotics

- Bactericidal activity
- Good oral bioavailability
- Good bone penetration
- Activity against biofilms
Bactericidal activity

# How much comes to surgical site?

<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><strong>Levofloxacin</strong></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. 45\(^{\text{nd}}\) ed.  
Lorian. Antibiotics in Laboratory Medicine. 5\(^{\text{th}}\) ed.
### EMPFOHLENE ANTIBIOTIKATHERAPIE

#### Empirische Antibiotikatherapie:
- Amoxicillin/Sulbactam* 3 x 3 g i.v.
  - (+/- Vancomycin* 2 x 1 g bei septischen Patienten, bekannten MRSA-Trägern, multiplen Vorerkrankungen und Vd. a. Low-Grade Infekt)

#### Gezielte Antibiotikatherapie (Deeskalation, sobald Pathogen(e) bekannt):

<table>
<thead>
<tr>
<th>Mikroorganismus</th>
<th>Antibiotikum*</th>
<th>Dosis* (blau: Nierenadaptation notwendig)</th>
<th>Gabe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus spp.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oxacillin/-Methicillin-empfindlich</td>
<td>Fluclaxolin*</td>
<td>4 x 2 g (i.v.)</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>(oder Fosfomycin)</td>
<td>(3 x 5 g)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ Rifaxpin*</td>
<td>2 x 450 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>für 2 Wochen, dann (je nach Antibrogramm)</td>
<td>2 x 550 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>- Levofloxacin oder</td>
<td>2 x 100 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>- Cotrimoxazol oder</td>
<td>2 x 100 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>- Doxycyclin oder</td>
<td>3 x 500 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>+ Rifaxpin*</td>
<td>2 x 450 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>Daptomycin oder</td>
<td>1 x 6 mg/kg</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>Vancomycin*</td>
<td>2 x 1 g</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>(oder Fosfomycin)</td>
<td>(3 x 5 g)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ Rifaxpin*</td>
<td>2 x 450 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td>- Oxacillin/-Methicillin-resistent</td>
<td>für 2 Wochen, dann, in Kombination wie oben für Oxacillin/-Methicillin-empfindliche Staphylokokken</td>
<td>2 x 550 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td><strong>Streptococcus spp.</strong></td>
<td>Penicillin G oder</td>
<td>4 x 5 Millionen U</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>Ceftaxoxin</td>
<td>1 x 2 g</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>für 2-4 Wochen, dann, Langzeitabnahme für ≥ 1 Jahr, abhängig von Empfindlichkeit (z.B. mit Cotrimoxazol, Doxycyclin oder Clarithromycin)</td>
<td>3 x 1000 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td><strong>Enterococcus spp.</strong></td>
<td>Ampicillin*</td>
<td>4 x 2 g</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>Gentamicin*</td>
<td>2 x 60-80 mg</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>(+/- Fosfomycin)</td>
<td>(3 x 5 g)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>für 2-3 Wochen, dann,</td>
<td>3 x 1000 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>- Amoxicillin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin* oder</td>
<td>2 x 1 g</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>Daptomycin</td>
<td>1 x 10 mg/kg</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>+ Gentamicin*</td>
<td>2 x 60-80 mg</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>(+/- Fosfomycin)</td>
<td>(3 x 5 g)</td>
<td></td>
</tr>
<tr>
<td>- Penicillin-resistant</td>
<td>für 2-4 Wochen, dann, Lineozolid (max. 4 Wochen)</td>
<td>2 x 600 mg</td>
<td>p.o.</td>
</tr>
</tbody>
</table>

#### Mikroorganismus (Erlaubtes/Weiterempfehlung)

<table>
<thead>
<tr>
<th>Antibiotika* (Empfindlichkeit überprüfen)</th>
<th>Dosis* (blau: Nierenadaptation notwendig)</th>
<th>Gabe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gramnegative Erreger</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Enterobacteriaceae (E. coli, Klebsiella, Enteroabakter etc.)</td>
<td>Ciproflaxacin</td>
<td>2 x 750 mg</td>
</tr>
<tr>
<td>- Nonfermenter (Pseudomonas aeruginosa, Acinetobacter spp.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Tobramycin (oder Gentamicin)</td>
<td>1 x 300 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td>für 2-4 Wochen, dann,</td>
<td>Ciproflaxacin</td>
<td>2 x 750 mg</td>
</tr>
<tr>
<td><strong>Ciproflaxacin-resistant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abhängig vom Antibiotogramm: Meropenem i.v. 3 x 1 g, Collin 3 x 3 Mic E i.v. und/oder Fosfomycin 3 x 5 g i.v., dann orale Suppression</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anaerobier</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Gram-positiv (Propionibacterium, Peptostreptococcus, Finegoldia magna)</td>
<td>Penicillin G oder</td>
<td>4 x 5 Millionen E</td>
</tr>
<tr>
<td>+ Ceftraxoxin</td>
<td>1 x 2 g</td>
<td>i.v.</td>
</tr>
<tr>
<td>für 2 Wochen, dann, Levofloxacin oder</td>
<td>2 x 500 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>3 x 1000 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td><strong>Gram-negativ</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ampicillin/Sulbactam*</td>
<td>Rifaxpin*</td>
<td>2 x 450 mg</td>
</tr>
<tr>
<td>(oder Fosfomycin)</td>
<td>für 2 Wochen, dann, Levofloxacin oder</td>
<td>2 x 500 mg</td>
</tr>
<tr>
<td>- Metronidazol</td>
<td>3 x 400 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td><strong>Candida spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Fluconazol-empfindlich</td>
<td>Caspofungin oder</td>
<td>1 x 50 mg (1. Tag 70 mg)</td>
</tr>
<tr>
<td>- Anidulafungin</td>
<td>1 x 100 mg (1. Tag 200 mg)</td>
<td>i.v.</td>
</tr>
<tr>
<td>für 2-4 Wochen, dann, Fluconazol (Suppression für ≥ 1 Jahr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fluconazol-resistant</strong></td>
<td>Individuell (z.B. mit Voriconazol 2 x 200 mg p.o.), Entfernung des Implantates oder ggf. lebenslange Suppression</td>
<td></td>
</tr>
<tr>
<td><strong>Kultur-negativ</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ampicillin/Sulbactam*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Levofloxacin oder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Rifaxpin*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Gesamtdauer der Therapie: 12 Wochen, ca. 2 Wochen Intravenös (i.v.) dann oral (p.o.)
1. Laborkontrolle: Leukozyten, C-reactives Protein, Kreatinin/GFR, Leberenzyme (AST/GOT und ALT/GPT). Dosisanpassung nach Nierenfunktion und Körpergewicht (< 60 kg oder > 100 kg)
2. Penicillin-Arroliergie von NICHT-Typ 1 (z.B. Exanthen, Cefazolin (3 x 2 g i.v.) bei Anaphylaxie (= Typ-I-Arroliergie mit Quinke-Ödem, Bronchospasmsus, anaphylaktischem Schock) oder Cefalosporin-Arroliergie: Vancomycin (2 x 1 g i.v.) oder Daptomycin (1 x 8 g i.v.). Ampicillin/Sulbactam ist identisch zu Amoxicillin/Cavansulure (3 x 2,2 g i.v.).
3. Rifamycin erst nach Prothesen-Wiederaufbau und bei trockenen Wundverhältnissen bzw. gezogenen Drainagen einsetzen; Dosiseinstellung auf 2 x 300 mg bei Alter > 75 Jahre
4. Bestimmung des Vancomycin-Talspiegels mindestens 1 x/Woche, Blutabnahme unmittelbar vor nächster Gabe. Zielwert: 15-20 µg/ml
5. Gentamicin nur anwenden, wenn Gentamicin High-level (HL) empfindlich getestet wird (im Mikrobiologie-Labor nachfragen). Bei Gentamicin HL-resistenten Enterokokken: Gentamicin durch Ceftaxoxin (1 x 2 g i.v.) ersetzen.
Diagnosis and Treatment of Prosthetic Joint Infection

Definition

Diagnosis of periprosthetic joint infection is confirmed if at least 1 criteria is fulfilled:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus tract (fluid) or visible pus in soft tissue around the prosthesis</td>
<td>20–30%</td>
<td>100%</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute inflammation in periprosthetic tissue (&gt;10 neutrophils per HPF) (Morawietz &amp; Keehn et al.)</td>
<td>95–99%</td>
<td>99–99%</td>
</tr>
<tr>
<td>Cytology*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2000/µl leukocytes or &gt; 70% granulocytes</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>Microbiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Bacterial growth in synovial fluid</td>
<td>80–90%</td>
<td>97%</td>
</tr>
<tr>
<td>- a2 periprosthetic tissue samples**</td>
<td>70–85%</td>
<td>92%</td>
</tr>
<tr>
<td>- Suction fluid (≤ 50 CFU/ml)</td>
<td>85–95%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Note: Local inflammation within 6 weeks after surgery, in the absence of infection, can appear to obscure evidence for infection. In such cases, further investigation is necessary (e.g., aspiration, biopsies, tissue culture or other diagnostic tests).
Antibiotics with biofilm-activity

- **Staphylococci**: rifampin (in combination)
- **Gram-negative rods**: ciprofloxacin
- **Streptococci**: penicillin G (amoxicillin p.o.)
- **Enterococci**: ampicillin + gentamicin
Rifampin – precious but delicate
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

Efficacy in the guinea pig model (MRSA)

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

Rifampin resistance rate

Where is the evidence?

- Guidelines
- Systematic reviews / Metaanalysis
- Level I: Randomised controlled trials
- Level II: Cohort studies
- Level III: Case-control studies
- Level IV: Case series, case reports
- Level V: Expert opinion

CMSC
Centrum für Muskuloskeletale Chirurgie

CHARITÉ

JULIUS WOLFF INSTITUT
Staphylococcal implant infections

Prospective on Rifampin

Historical - rifampin

Historical - non-rifampin

Survival free of treatment failure (%)

Months

El Helou et al. EJCMID 2010
History of rifampicin

• Inhibits DNA-dependent RNA polymerase.
• 1957: new substance as 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”).
Rififi: a 1955 French crime film

Adaptation of Auguste le Breton's novel. Jules Dassin earned the award for Best Director at the 1955 Cannes Film Festival.

"I liked you Macaroni. But you know the rules..."
Diagnosis
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
Systemic and local antibiotics

Concentrations of antibiotics after systemic application (1x80mg i.m. gentamicin) and local application (1.25% gentamicin in PMMA)

→ 10-100-fold local concentration!
→ Minimal systemic effects

Wahlig 1987, Kühn D., Unfallchirurg, 2017
Background: systemic vs local release

Systemic release:
- High local concentrations
- No systemic toxicity
- Low serum levels
- Low urine levels
- Systemic toxicity*

Local release:
- High local concentrations
- No systemic toxicity
- Low serum levels
- Low urine levels

*oto- and nephrotoxicity for aminoglycosides

Berberich 2017
PMMA + Amphotericin B

copolymethylmethacrylate + vs. Candida spp.
Background: local antimicrobial treatment

Degradable biomaterials

Natural polymers
- Collagen
- Hyaluronic acid
- Chitosan

Synthetic polymers
- HPMAm
- PLGA
- PLA

Ceramics/inorganic compounds
- Bioactive glass ($\text{SiO}_2$)
- Hydroxyapatite
- $\text{Ca}_3(\text{PO}_4)_2$
- $\text{CaSO}_4$

Biomaterial → Loaded ABX → ABX release + biomaterial degradation
Antibiofilm surface

Biofilm formation

Cooperation partner:
• Freie Universität, Berlin

25-30 kinds of mussel foot proteins
Injectable thermosensitive hydrogels

Physical cross-linking (thermal gelation)

Chemical cross-linking

- HA−SH \xrightarrow{\text{SO}} \xleftarrow{-\text{H}^+} HA−S−C−\text{SO}
- HA−S−C−\text{SO} \xrightarrow{+\text{H}^+} \xleftarrow{\text{SO}} HA−SH
Click & Release project

A Local hydrogel injection

B Pro-Drug iv. injection

C Drug concentration

D Drug release

Antibiotics:
- vancomycin
- daptomycin

Cooperation partners:
- University of California, Davis
- New York University at Albany
New options?
Timeline of antibiotic discovery

**Natural origin**
- Sulfa drugs
- Para-aminosalicylic acid
- Penicillin
- Streptomycin
- Chloramphenicol
- Tetracycline
- Isoniazid
- Cephalosporins
- Kanamycin
- Vancomycin, erythromycin, trimethoprim, metronidazole

**Synthetic origin**
- Ampicillin, penicillin analogues
- Tetracycline analogues
- Methicillin
- Gentamicin
- Tobramycin
- Amikacin
- Cephalosporins
- Clavulanic acid

**1940**
- Natural product screening

**1960**
- Natural product screening

**2000**
- Genomics, screening, crystallography, de novo design, natural product template
- Genomics, chemical library screening

**1980**
- Antibiotic analogues
- Other fluoroquinolones
- Erythromycin analogues
- Teicoplanin
- Ciprofloxacin
- Imipenem
- Aztreonam

Fernandes P. *Nature Biotechnology* 2006;24:1497–1503
Prevention
Perioperative prevention

Antibiotic prophylaxis

Desinfection of the skin

Patient-related risk factors

Future: vaccination
<table>
<thead>
<tr>
<th></th>
<th>Orthopaedic surgeries</th>
<th>Cardio-thoracic surgeries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>RR (CI95) %</td>
</tr>
<tr>
<td>Randomised studies</td>
<td>2</td>
<td>0.48 (0.18-1.28)</td>
</tr>
<tr>
<td>Non-randomised studies</td>
<td>5</td>
<td>0.59 (0.42-0.82)</td>
</tr>
<tr>
<td>All studies(^1)</td>
<td>7</td>
<td>0.57 (0.42-0.79)</td>
</tr>
</tbody>
</table>

\(^1\) „treat-all“ und „screen and treat“

Efficacy

Prospective, randomised placebo-controlled trial, >1000 patients

Bode et al. NEJM 2010

Table 2. Relative Risk of Hospital-Acquired Staphylococcus aureus Infection and Characteristics of Infections (Intention-to-Treat Analysis).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mupirocin–Chlorhexidine (N = 504)</th>
<th>Placebo (N = 413)</th>
<th>Relative Risk (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus infection</td>
<td>17 (3.4)</td>
<td>32 (7.7)</td>
<td>0.42 (0.23–0.75)</td>
</tr>
<tr>
<td>Source of infection†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endogenous</td>
<td>12 (2.4)</td>
<td>25 (6.1)</td>
<td>0.39 (0.20–0.77)</td>
</tr>
<tr>
<td>Exogenous</td>
<td>4 (0.8)</td>
<td>6 (1.5)</td>
<td>0.55 (0.16–1.92)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Localization of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep surgical site‡</td>
<td>4 (0.9)</td>
<td>16 (4.4)</td>
<td>0.21 (0.07–0.62)</td>
</tr>
<tr>
<td>Superficial surgical site‡</td>
<td>7 (1.6)</td>
<td>13 (3.5)</td>
<td>0.45 (0.18–1.11)</td>
</tr>
<tr>
<td>Lower respiratory tract</td>
<td>2 (0.4)</td>
<td>2 (0.5)</td>
<td>0.82 (0.12–5.78)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>1 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Soft tissue</td>
<td>2 (0.4)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Relative risks are for S. aureus infection in the mupirocin–chlorhexidine group.
† The source of the S. aureus infections was determined by comparing nasal strains with strains isolated from the infection site by pulsed-field gel electrophoresis.
‡ Data are for surgical patients only: 441 in the mupirocin–chlorhexidine group and 367 in the placebo group.
Decolonization

- Distribution of a kit in the outpatients clinic to all patients planned for elective surgery with implantation of hardware (treat-all)
- 5 days body wash and application of nasal ointment
Staphylococcus aureus 4-Antigen Vakzine

Indikation: Elektive Wirbelsäule-Stabilisierung

Studie
Phase 2b, randomisiert, doppel-blind, Plazebo-kontrolliert (erwartet wird Reduktion der SSI um 50-70%)

Intervention
Eine Dosis: 10-60 Tage vor OP
### S. aureus Vaccine (SA4Ag) is Designed To Target Multiple Virulence Mechanisms

<table>
<thead>
<tr>
<th>Virulence Mechanism</th>
<th>Target Antigens</th>
<th>Functional Immunoassay(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-phagocytic</td>
<td>Capsular polysaccharides (CP5 and CP8): CP5-CRM197, CP8-CRM197</td>
<td>OPA, cLIA</td>
</tr>
<tr>
<td>Adhesion to host factors</td>
<td>Clumping factor A (ClfA): rmClfA</td>
<td>FBI, cLIA</td>
</tr>
<tr>
<td>Divalent cation scavenging (nutrient acquisition)</td>
<td>Manganese transporter C (MntC): rP305A</td>
<td>cLIA</td>
</tr>
</tbody>
</table>

- Selected antigens elicit immune responses targeting surface-expressed, conserved, and globally represented *S. aureus* components expressed during infection.
- Being investigated to determine if it’s broadly protective across the range of clinical *S. aureus* disease isolates regardless of their antibiotic resistance profiles or geographic origin.

---

2 Rozemeijer W, et al. *ICAAC* 2012 (G-870);
SA4Ag Elicits a Rapid and Sustained Immune Response through Month 12

SA4Ag includes 30 µg of CP5-CRM₁₉₇, 30 µg of CP8-CRM₁₉₇, 60 µg of rmClfA, and 200 µg of rP305A (MntC).

SA4Ag Phase 1/2 safety and immunogenicity study: 18-64 years
Bacteriophages vs Biofilm

Tamta Tkhilaishvili, MD
Who are they?

• The most numerous form of life

• Lytic vs Lysogenic phages

Only Lytic Phages can be used for Phage Therapy !!!
Sb-1 and Pyo-phage
Pyo-Phage was not active against these isolates.
Phage AbkG against MRSA biofilm

Real time antibiofilm activity

![Graph showing real time antibiofilm activity for different initial bacterial concentrations.](chart1)

Biofilm eradication

![Graph showing biofilm eradication for different initial bacterial concentrations.](chart2)

Charité – Universitätsmedizin Berlin
Phage isolation

- **Sources**: Human saliva, sewage, river water
- **Clinical strains used as hosts**: *S. aureus*, *S. epidermidis* and *E. coli* strains from PJI patients

Isolation of bacteriophages displaying lytic antibacterial activity from the plaque of lysis

Evaluation of the susceptibility of a panel of clinical isolates to newly isolated phages (spot-assay)
Acknowledgements
Ortho/trauma surgeons

Researchers

ID/microbiology

Septic surgery unit

Observers
CONSULTATION SERVICE PORTAL
www.pro-implant-foundation.org

NEW
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

Centrum Muskulo Skeletale Chirurgie
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.

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PRO-IMPLANT Foundation accepts no liability for the content or the consequences of any actions taken on the basis of the advice provided. The received information is treated confidentially.
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