New Strategies in Diagnosis and Treatment of Infection of the Shoulder

Andrej Trampuz
Charité – University Medicine Berlin
Germany
Implants improved life quality
## 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
Modern concepts
Key to success: Target the biofilm

- Diagnosis
- Antibiotics
- Surgery

Cure rate > 90%

Directed against biofilms
Planktonic bacteria & granulocytes
Biofilm

- Adherent to surface (min-h)
- Embedded in matrix (70%)
- Slowly replicating (stationary phase)
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 (fistula) or visible</td>
<td>20-50%</td>
<td>100%</td>
</tr>
<tr>
<td>Pannus around the prosthesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute inflammation in periprosthetic tissue (&gt;10 neutrophils per HPF) (Mortelnet &amp; Krein 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/l leukocytes or &gt; 70% granulocytes</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>Microbiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbial growth in:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>80-85%</td>
<td>97%</td>
</tr>
<tr>
<td>a2 periarticular tissue samples</td>
<td>70-85%</td>
<td>92%</td>
</tr>
<tr>
<td>Suction fluid (≥ 50 CFI/mL)</td>
<td>85-95%</td>
<td>95%</td>
</tr>
</tbody>
</table>

*may also occur within 6 weeks after surgery, in hematoma post dislocation, prosthesis fracture or presumed infection (e.g. S. aureus, S. epidermidis or cohesive S. epidermidis colonies)
1. Low-grade infections

100,000 bacteria/cm²

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

- **Anaerobes**
  - *Cutibacterium acnes*

Normal skin flora
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 postoperative</td>
<td>Delayed (low grade)</td>
<td>Late</td>
</tr>
<tr>
<td>Route</td>
<td>Perioperative</td>
<td>Haematogenous</td>
<td></td>
</tr>
<tr>
<td>Signs</td>
<td>Acute: effusion, warmth, dehiscence</td>
<td>Chronic: Persistent pain, loosening, sinus tract</td>
<td>Acute: fever, rigor, acute joint pain</td>
</tr>
<tr>
<td>Pathogen</td>
<td>S. aureus Streptococci Enterococci</td>
<td>Staph. epidermidis Cutibacterium acnes</td>
<td>S. aureus E. coli Streptococci</td>
</tr>
</tbody>
</table>
History: age of the prosthesis

Kaplan-Meier analysis of 112 prostheses

Survival probability (%)

- 16%
- 69%

P<0.001

2 years

Portillo ME, CORR 2013
Definition

Was is an infection?
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
- Production errors, improper materials or design
- Acute mechanical overload
- Chronic mechanical overload
- Bone to implant interface failure
- Effective joint space fluid pressure
- Implant positioning, poor approach
- Preoperative diagnosis
- Complication rate
- Poor surgical technique
- Poor education, low surgical volume

- Wear particles
- Infection
- Periprosthetic fracture
- Osteolysis
- Hypersensitivity, mutagenicity?
- Metal ion release
- Excessive micromotion
- Bone to implant toughness mismatch
- Excessive rigidity
- Unnatural force transfer
- Stress shielding, weak bone
- Systemic alterations
- MOP, MOM, COC bearing couples
- Aggressive activity - sports
- RANK, RANKL, OPG
- MOM, micromotion, lymphocyte activation
- Production errors, improper materials or design

- Effective joint space fluid pressure
- Implant positioning, poor approach
- Complication rate
- Poor surgical technique
- Poor education, low surgical volume

- Excessive rigidity
- Unnatural force transfer
- Stress shielding, weak bone
- Systemic alterations
- MOP, MOM, COC bearing couples
- Aggressive activity - sports
- RANK, RANKL, OPG
- MOM, micromotion, lymphocyte activation
- Production errors, improper materials or design
Is it an infection?

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

In humans: Avoid an apparently risky situation by pretending it doesn’t exist.

The ostrich effect
ICM – PJI Algorithmus

Major criteria (at least one of the following)

| Two positive growth of the same organism using standard culture methods | Infected |
| Sinus tract with evidence of communication to the joint or visualization of prosthesis |

<table>
<thead>
<tr>
<th>Minor criteria</th>
<th>Acute</th>
<th>Chronic</th>
<th>Score</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum CRP (mg/L) or D-Dimer (μg/L)</td>
<td>100</td>
<td>10</td>
<td>2</td>
<td>Combined preoperative and postoperative score:</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>860</td>
<td></td>
<td>≥ 6 infected</td>
</tr>
<tr>
<td>Elevated Serum ESR (mm/hr)</td>
<td>No role</td>
<td>30</td>
<td>1</td>
<td>4-5 Inconclusive*</td>
</tr>
<tr>
<td>Elevated Synovial WBC (cells/μL) or Leukocyte Esterase or Positive Alpha Defensin (signal/cutoff)</td>
<td>10,000</td>
<td>3,000</td>
<td>3</td>
<td>≤3 Not infected</td>
</tr>
<tr>
<td></td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated Synovial PMN (%)</td>
<td>90</td>
<td>70</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Single Positive Culture</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Positive Histology</td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Positive Intraoperative Purulence</td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis of periprosthetic joint infection is confirmed if at least 1 criteria is fulfilled:

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<th>Criteria</th>
<th>Sensitivity</th>
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<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus tract (fistula) or visible purulence around the prosthesis</td>
<td>20-30%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Cytology in synovial fluid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&gt;2000/\mu l) leukocytes or (\geq 70%) granulocytes</td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation in periprosthetic tissue ((&gt;23) granulocytes per 10 HPF after Morawietz &amp; Krenn)</td>
<td>73%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Microbiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbial growth in:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Synovial fluid</td>
<td>45-75%</td>
<td>95%</td>
</tr>
<tr>
<td>• (\geq 2) periprosthetic tissue samples*</td>
<td>60-80%</td>
<td>92%</td>
</tr>
<tr>
<td>• Sonication fluid ((\geq 50) CFU/ml)</td>
<td>80-90%</td>
<td>95%</td>
</tr>
</tbody>
</table>

*For highly virulent organisms (e.g. S. aureus, E. coli) 1 positive tissue sample is sufficient.
如果满足以下≥1标准，可诊断为假体周围感染:

<table>
<thead>
<tr>
<th>测试</th>
<th>准则</th>
<th>灵敏度</th>
<th>特异度</th>
</tr>
</thead>
<tbody>
<tr>
<td>临床表现</td>
<td>窦道（瘘管）形成或假体周围有明显的脓液形成&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20-30%</td>
<td>100%</td>
</tr>
<tr>
<td>组织学</td>
<td>假体周围组织出现急性炎症&lt;sup&gt;b&lt;/sup&gt;</td>
<td>95-98%</td>
<td>98-99%</td>
</tr>
<tr>
<td>关节腔穿刺液细胞计数&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&gt;2000/μL 白细胞或 &gt;70% 粒细胞（中性粒细胞）</td>
<td>93-96%</td>
<td>97-98%</td>
</tr>
<tr>
<td>微生物学</td>
<td>微生物生长于：</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-关节液</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-至少2份组织样本&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-超声冲洗液(≥50 CFU/ml)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>60-80%</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70-85%</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>85-95%</td>
<td>95%</td>
</tr>
</tbody>
</table>

<sup>a</sup>窦道（瘘管）形成或假体周围有明显的脓液形成；
<sup>b</sup>假体周围组织出现急性炎症；
<sup>c</sup>关节腔穿刺液细胞计数；
<sup>d</sup>至少2份组织样本；
<sup>e</sup>超声冲洗液(≥50 CFU/ml)。
Диагноз перипротезной инфекции подтверждается при наличии одного и более критериев

<table>
<thead>
<tr>
<th>Тест</th>
<th>Критерии</th>
<th>Чувствительность</th>
<th>Специфичность</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Клинические признаки</strong></td>
<td>Свищ или видимое нагноение тканей вокруг протеза(^1)</td>
<td>20-30%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Гистология</strong></td>
<td>Острое воспаление перипротезной ткани(^2)</td>
<td>95-98%</td>
<td>98-99%</td>
</tr>
<tr>
<td><strong>Цитология синовиальной жидкости</strong></td>
<td>&gt; 2000/мкл лейкоцитов(^3) или_  &gt; 70% гранулоцитов (ПЯН)</td>
<td>93-96%</td>
<td>97-98%</td>
</tr>
</tbody>
</table>
| **Микробиология**          | Рост микроорганизмов в:
  • синовиальной жидкости или_
  • ≥2 биоптатах\(^4\) или_
  • концентрационной жидкости (≥50 КОЭ/мл)\(^5\)                   | 60-80%          | 97%           |
  |                             |                                                                          | 70-85%          | 92%           |
  |                             |                                                                          | 85-95%          | 95%           |
Conclusion

Early loosening (<2 years of implantation) and/or persistent pain
=> highly suggestive for infection!
2. Diagnostic algorithm in PJI

- Clinical examination
- Laboratory testing (CRP)
- X-ray (prosthesis)

Sinus tract (permanent or temporary)?

Joint aspiration:
- Leukocyte count/differential
- Microbiology (culture)

Leukocyte count or culture consistent with infection?

Other reasons excluded?

Persistent suspicion of infection or high level of suffering?

Repeat diagnostic aspiration 3 months later

Consider arthroscopic or open biopsy

Septic revision of prosthesis with intraoperative diagnostics

Consider other reasons:
- Aseptic loosening
- Periprosthetic fracture
- Dislocation
- Muscular pathology
- Wear of bearing components
- Metallosis
- Other

Leukocyte count or culture consistent with infection?

Yes

PKI Pocket Guide V8 (2018)
preoperative

History & clinical presentation

laboratory

imaging

intraoperative

intraoperative sampling

microbiology histopathology

sonication

joint puncture

cytology microbiology histopathology

sonication

cytology microbiology histopathology
Joint aspiration

- Microbiology
- Leukocyte count
Cutibacterium: Time to culture positivity

Prolonged incubation increased culture positivity considerably

40% 20%
**Cutibacterium: Synovial fluid leukocyte count**

### Positivity rate: 19/26 (73%)

<table>
<thead>
<tr>
<th>I</th>
<th>Sex, age</th>
<th>Joint</th>
<th>CRP (mg/l)</th>
<th>Microbio (positive specimen)</th>
<th>Pathology</th>
<th>Sinus tract</th>
<th>temporal appearance (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>F, 72</td>
<td>Hip</td>
<td>5,6</td>
<td>S, T (1/2)</td>
<td>Neg.</td>
<td>no</td>
<td>30</td>
</tr>
<tr>
<td>b</td>
<td>F, 73</td>
<td>Knee</td>
<td>0,6</td>
<td>T (2/5)</td>
<td>Neg.</td>
<td>no</td>
<td>25</td>
</tr>
<tr>
<td>c</td>
<td>F, 76</td>
<td>Hip</td>
<td>44,4</td>
<td>S</td>
<td>Pos.</td>
<td>no</td>
<td>98</td>
</tr>
<tr>
<td>d</td>
<td>F, 51</td>
<td>Knee</td>
<td>14,6</td>
<td>SF</td>
<td>NA</td>
<td>no</td>
<td>11</td>
</tr>
<tr>
<td>e</td>
<td>F, 79</td>
<td>Knee</td>
<td>9,3</td>
<td>SF</td>
<td>Pos.</td>
<td>no</td>
<td>NA</td>
</tr>
<tr>
<td>f</td>
<td>M, 71</td>
<td>Hip</td>
<td>0,7</td>
<td>S, T (2/5)</td>
<td>Neg.</td>
<td>no</td>
<td>324</td>
</tr>
</tbody>
</table>

S, sonication; SF, synovial fluid; T, tissue

Renz N et al. PLoS 2018
## Alternative tests in synovial fluid?

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-defensin (lateral flow test)</td>
<td>67%</td>
<td>93%</td>
</tr>
<tr>
<td>Leukocyte esterase</td>
<td>81%</td>
<td>97%</td>
</tr>
<tr>
<td>D-Lactate</td>
<td>94%</td>
<td>98%</td>
</tr>
<tr>
<td>Multiplex-PCR</td>
<td>60%</td>
<td>89%</td>
</tr>
</tbody>
</table>

Kasparek MF, JA 2016

Wyatt MC, JBJS 2016

Karbysheva S, personal communication

Morgenstern C, DMID, 2017
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>
**Results:** Of 212 included patients, 151 (71%) had a knee prosthesis and 61 (29%) had a hip prosthesis. PJI was diagnosed in 45 patients (21%) using the MSIS criteria, in 55 patients (26%) using the IDSA criteria and in 79 patients (37%) using the proposed EBJIS criteria. The sensitivity of the ADLF test was 84% (95% confidence interval [CI], 71% to 94%) with the MSIS criteria, 67% (95% CI, 53% to 79%) with the IDSA criteria, and 54% (95% CI, 43% to 66%) with the proposed EBJIS criteria. The ADLF test showed high specificity using all classification criteria (96% to 99%) and represented the most specific preoperative test for PJI, especially in the early postoperative period (91%; 95% CI, 59% to 100%). Using the proposed EBJIS definition criteria, the sensitivity of the leukocyte count was significantly higher than that of the ADLF test (86% [95% CI, 76% to 93%] compared with 54% [95% CI, 43% to 66%]; p < 0.001), particularly in chronic PJI (81% compared with 44%, respectively; p < 0.001).

**Conclusions:** The ADLF test was rapid and highly specific for diagnosing PJI (>95%). However, its sensitivity was limited (54% to 84%) and it should therefore not be used for screening, but rather as a confirmatory test for PJI.

**Level of Evidence:** Diagnostic Level I. See Instructions for Authors for a complete description of levels of evidence.
## Demographics and infection characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median patient age (range)</td>
<td>70 years (41-94)</td>
</tr>
<tr>
<td>Female gender, no (%)</td>
<td>106 (50)</td>
</tr>
<tr>
<td>Joint</td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>151 (71)</td>
</tr>
<tr>
<td>Hip</td>
<td>61 (29)</td>
</tr>
<tr>
<td>Timing of joint aspiration after primary surgery, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Early (&lt;3 months)</td>
<td>33 (16)</td>
</tr>
<tr>
<td>Delayed (3-24 months)</td>
<td>79 (37)</td>
</tr>
<tr>
<td>Late (&gt;24 months)</td>
<td>100 (47)</td>
</tr>
<tr>
<td>Patients undergoing revision surgery after joint aspiration</td>
<td>146 (69)</td>
</tr>
</tbody>
</table>
Applying proposed EBJIS criteria, which allow detection of low-grade infections, sensitivity of alpha defensin lateral flow test was 54% with a high specificity of 99%
Synovial fluid multiplex PCR is superior to culture for detection of low-virulent pathogens causing periprosthetic joint infection

Christian Morgenstern a, Sabrina Cabric a,b, Carsten Perka a,b, Andrej Trampuz a,b, Nora Renz a,*

a Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Center for Musculoskeletal Surgery (CMSC), Berlin, Germany
b Berlin-Brandenburg Center for Regenerative Therapies, Berlin, Germany

<table>
<thead>
<tr>
<th></th>
<th>PCR +</th>
<th>PCR -</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Culture +</strong></td>
<td>33</td>
<td>S. aureus (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. mitis/oralis (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E. coli (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E. faecalis (1)</td>
</tr>
<tr>
<td><strong>Culture -</strong></td>
<td>C. acnes (4)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>CNS (6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P. aeruginosa (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S. pyogenes (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abiotrophia spp. (1)</td>
<td></td>
</tr>
</tbody>
</table>

![Graph](image1.png)

- Sensitivity
- Specificity

- Leukocyte count (n=103)
- Culture (n=142)
- PCR (n=142)
Sonication of Removed Hip and Knee Prostheses for Diagnosis of Infection

Sonication of implants

Sonication – biofilm bacteria
Sonication – biofilm bacteria

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

Tissue biopsy  Sonication fluid
Treatment
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!
### Treatment algorithm

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

  - Yes: Débridement & retention, exchange of mobile parts
  - No: Prosthesis exchange

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

  - No: One-stage exchange
  - Yes: Two-stage exchange

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

  - No: Short interval (2-3 weeks)
  - Yes: Long interval (6-8 weeks)

**Three-stage exchange**

Long-term suppressive antibiotic therapy, permanent arthrodesis/girdlestone

Eradication of infection not possible

**DTT** = difficult-to-treat infections caused by pathogens resistant to biofilm-active antimicrobials
- Rifampin-resistant staphylococci
- Ciprofloxacin-resistant gram-negative bacteria
- Fungi (Candida)
Retention of fixed prosthetic components

- One-stage exchange
  - Change of mobile parts: 2 weeks
  - Explantation & Implantation: 10 weeks

- Two-stage exchange (short interval)
  - Change of mobile parts: 2 weeks, 1 week
  - Explantation & Implantation: 9 weeks

- Two-stage exchange (long interval)
  - Change of mobile parts: 2 weeks, 4 weeks, 1 week
  - Explantation & Implantation: 5 weeks

- Three-stage exchange
  - Change of mobile parts: 3 weeks, 3 weeks, 1 week
  - Explantation & Implantation: 5 weeks

**Intervention**
- 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

**Antibiotics (total 12 weeks)**

**Biofilm treatment**
Treatment concept of PJI: 1998-2009

- Acute infections (<3 weeks of symptoms)
- Stable prosthesis
- Good soft tissue
- No difficult to treat organism (see below)

**Difficult-to-treat organism?**

- Yes
  - Rifampin-R staphylococcus
  - Ciprofloxacin-R Gram- rods
  - Fungi
  - Debridement and retention

- No
  - One stage
    - Explantation and implantation
  - Two stage (short interval)
    - Explantation
    - Implantation
    - 2-3 weeks i.v.
  - Two stage (long interval)
    - Explantation
    - Implantation
    - 6 weeks i.v.

- No treatment

**Debridement**

- 2 weeks i.v.
- 10 weeks p.o.

**“Biofilm treatment”** (with rifampin if applicable)

**“Osteomyelitis treatment”** (no rifampin)
Properties of antibiotics

- Bactericidal activity
- Good oral bioavailability
- Good bone penetration
- Activity against biofilms
Antibiotics with biofilm-activity

- **Staphylococci**: rifampin (in combination)
- **Gram-negative rods**: ciprofloxacin
- **Streptococci**: penicillin G (amoxicillin p.o.)
- **Enterococci**: ampicillin + gentamicin
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>Levofloxacin</td>
<td>100%</td>
<td>77%</td>
</tr>
<tr>
<td>Rifampin</td>
<td>80%</td>
<td>51%</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>95%</td>
<td>64%</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>

**Targeted therapy**

---

### Empfohlene Antibiotikatherapie

#### Empirische Antibiotikatherapie:
- Ampicillin/Sublactam 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>- Oxasillin/Methicillin-empfindlich</td>
<td>Fludoxacin</td>
<td>4 x 2 g</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>(oder Fosfomycin)</td>
<td>(3 x 5 g)</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
<td>2 x 450 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>für 2 Wochen</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(je nach Antibogramm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Levofoxacin</td>
<td>2 x 550 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>- Cotrimoxazol</td>
<td>3 x 960 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>- Doxycyclin</td>
<td>2 x 100 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>- Fusidinsäure</td>
<td>3 x 500 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</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>p.o.</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>2 x 1 g</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>(oder Fosfomycin)</td>
<td>(3 x 5 g)</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Rifampicin</td>
<td>2 x 450 mg</td>
<td>p.o.</td>
<td></td>
</tr>
<tr>
<td>- Daptomycin oder</td>
<td>1 x 6 mg/kg</td>
<td>p.o.</td>
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<td>- Vancomycin</td>
<td>2 x 1 g</td>
<td>p.o.</td>
<td></td>
</tr>
<tr>
<td>- (oder Fosfomycin)</td>
<td>(3 x 5 g)</td>
<td>p.o.</td>
<td></td>
</tr>
</tbody>
</table>

#### Anaerobier
- Gram-positiv (Propionibacterium, Peptostreptococcus, Finegoldia magna)
  - Rifampicin | 2 x 450 mg | p.o. |
  - für 2 Wochen | | |
- Gram-negativ (Propionibacterium, Peptostreptococcus, Finegoldia magna)
  - Metronidazol | 3 x 400 mg | p.o. |

### Mikroorganismus

<table>
<thead>
<tr>
<th>Mikroorganismus</th>
<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>
<td></td>
</tr>
<tr>
<td>- Enterobacteraceae (E. coli, Klebsiella, Enterobacter etc.)</td>
<td>Ciprofloxacin</td>
<td>2 x 750 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td>- Pseudomonas aeruginosa</td>
<td>Tetracyclin (oder Gentamicin)</td>
<td>3 x 4 g</td>
<td>i.v.</td>
</tr>
<tr>
<td>- Acinetobacter baehr</td>
<td>Tobramycin</td>
<td>3 x 1 g</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>für 2-3 Wochen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ciprofloxacin (oder Gentamicin)</td>
<td>1 x 300 mg</td>
<td>i.v.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>für 2-3 Wochen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cefazolin</td>
<td>1 x 240 mg</td>
<td>i.v.</td>
<td></td>
</tr>
</tbody>
</table>

### Candida spp.
- Fluconazol-empfindlich
  - Caspofungin oder | 1 x 50 mg (1 Tag 70 mg) | i.v. |
  - Anidulafungin | 1 x 100 mg (1 Tag 200 mg) | i.v. |
- Fluconazol-resistent
  - Individuell (z. B. mit Voriconazol 2 x 200 mg p.o.); Entfernung des Implantates oder ggfl. lebenslange Suppression

### Kultur-negativ
- Ampicillin/Sublactam | 3 x 3 g | i.v. |
- Levofoxacin | 2 x 500 mg | p.o. |
- Rifampicin | 2 x 450 mg | p.o. |
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
Local antibiotics in PMMA cement
Use of local antibiotics

Use of ALBC

Prevent biofilm formation

Prophylaxis

Low-dose ALBC
0.5 - 1 g antibiotic per 40 g cement

Primary and revision surgery

Prevent colonisation

Support eradication of infection

Treatment

High-dose ALBC
2-4 g antibiotic per 40 g cement

Septic revisions

Local therapy
Prevent colonisation
Combination: broad antimicrobial spectrum and better elution

Bone cement with gentamicin & clindamycin

Bone cement with gentamicin & vancomycin
Arthrofibrosis

Treatment after arthrolysis:

- **Antibiotic**: levofloxacin + rifampin (6 weeks)
  Targeting *Cutibacterium* & *Staphylococcus*)

- **Antiinflammatory**: Oral steroids (20 days)
  Prednisolone
  20 mg (5 d), 10 mg (5 d), 5 mg (5 d), 2,5 mg (5 d)
Shoulder stiffness / pain after arthroscopy

- **Inclusion:** arthrofibrosis within 12 months of arthroscopy
- **Exclusion:** previous surgery, clinical infection, implant
- **During revision arthroscopy:** tissue (synovial membrane, subacromial bursa) for histology & culture (14 days)
- **Results:** 37 patients, in 16 (43%) cultures grew *Cutibacterium* (n=12), CN staphylococci (n=8), both (n=6); among them in 7 (19%) additional adhesive capsulitis
- **Treatment:** all 16 received levofloxacin + rifampicin for 6 weeks, with capsulitis additional oral steroids for 20 days
- **Re-arthrofibrosis** in 5/21 (24%) w/o steroids/antibiotics, 2/16 (13%) with antibiotics, in 0/7 with antibiotics+ steroids

Pauly S et al. Unpublished
Workshop on Prosthetic Joint Infection (PJI)

Berlin, Germany

April 8–9, 2019
July 18–19, 2019
October 10–11, 2019
December 16–17, 2019

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 PORTAL
cs.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

Infections of the musculoskeletal system
Basic principles, prevention, diagnosis and treatment

Excerpt
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