ESSENTIALS IN DIAGNOSTICS OF PERIPROSTHETIC JOINT INFECTION (PJI)
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- Bacterial culture incubation
- Biofilm
- Blood tests
- Classification
- Definition of PJI
- Diagnostic algorithms
- Diagnostic methods
- Epidemiology
- History / clinical diagnosis
- Imaging
- Intraoperative diagnostics
- Intraoperative sampling
- Joint fluid aspiration
- Pathogenesis
- Preoperative diagnostics
- Risk factors
- Sonication
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- Therapeutic options
- Treatment algorithm

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- Checklist “low grade (delayed) infection”
- Checklist “acute haematogenous infection”
- Checklist “early postoperative infection”
- Checklist “Periprosthetic Joint Infection”
INTRODUCTION

Periprosthetic joint infection (PJI) is a serious complication in arthroplasty. Revision rates due to infection are constantly rising in parallel with the increasing number of primary procedures around the world. Other contributing factors to the increase of infection is the aging population with complicating comorbidities such as obesity, smoking, poor diet, to name just a few. Last but not least within the last years due to better diagnostic methods and algorithms many infections are identified which up to this point were classified as aseptic cases.

Diagnosis is the key to the successful management of PJI. But why is diagnostics of PJI so difficult? Even with new methods and improvements in the diagnostic procedure there is still no test which has 100% sensitivity or specificity. To diagnose PJI you always need a combination of different methods and the knowledge to interpret the results properly. The special microbial situation with biofilm forming and slow growing microorganisms makes it sometimes difficult to differentiate between infection and aseptic prosthesis failure. For successful diagnosis and treatment of PJI both the surgical and infection/microbiology perspectives have to be considered. So multidisciplinary teamwork is crucial.

It's all about combining the right methods at the right time, and the correct interpretation of the results.

The PALACADEMY ebook Essentials in diagnostics of Periprosthetic Joint Infection (PJI) supports orthopaedic surgeons and infectious disease specialists/physicians to a better diagnostic outcome in management of PJI by providing a practical guide through the diagnostic process in three main sections:

Section 1: Learning cases of the three main types of PJI offer a step-by-step presentation of the diagnostic process following real case studies.

Section 2: The most important Challenges within this process are discussed.

Section 3: Scientific background with literature and checklists are given in the Media Library.
With this ebook you will gain the ability to diagnose PJI following a steps-by-step process and differentiate between the various types of infection and their specialities (bacteria, biofilm, symptoms). Knowledge about established and new diagnostic methods helps to evaluate their advantages and disadvantages. You will learn correct sampling for microbiological testing and increased sensitivity and the handling of challenges to avoid most common mistakes in diagnosing PJI.
1. DIAGNOSTIC PROCESS – STEP-BY-STEP GUIDE

The three detailed learning cases in the following chapters cover the basic infection types according to the common PJI classification (low grade infection, acute haematogenous infection and early postoperative infection) with a step-by-step explanation of the diagnostic algorithm. Following the learning cases – from history and preoperative diagnostics to intraoperative methods – you get to know all the key facts and procedures which are relevant in diagnostics of PJI. Most important learning points are summarized at the end of every step. Links to the challenges and media library lead to related topics where you find scientific background information and can deepen your knowledge. References are listed at the end of every step.
1.1 Learning case 1: low grade infection

Case summary: Male; 60 years old

Low-grade infections are often difficult to diagnose. Is it an infection? In this learning case the patient had to suffer more than 2 years of diagnostic procedures without clear diagnosis or detection of a microorganism.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Morbus Parkinson</td>
</tr>
<tr>
<td>2008</td>
<td>Severe osteoarthritis of right knee</td>
</tr>
<tr>
<td>07/2008</td>
<td>Primary Implantation of Total knee Prosthesis</td>
</tr>
<tr>
<td>09/2009</td>
<td>Spondylodesis after transpedicular microdiscectomy L4/5</td>
</tr>
<tr>
<td>11/2009</td>
<td>Fever, Chills, CRP 123 mg/l (normal &lt; 5 mg/l), Knee prosthesis: painful, no effusion</td>
</tr>
<tr>
<td></td>
<td>Blood cultures: Staphylococcus aureus (MSSA)</td>
</tr>
<tr>
<td>12/2009</td>
<td>Removal of knee prosthesis and implantation of spacer with antibiotics (vancomycin 2 g/40 g PMMA)</td>
</tr>
<tr>
<td></td>
<td>Antibiotic treatment: flucloxacillin 4 x 2 g iv 6 weeks</td>
</tr>
<tr>
<td>01/2010</td>
<td>Surgery: reimplantation at 6 weeks</td>
</tr>
<tr>
<td></td>
<td>Antibiotic treatment: levofloxacin 2 x 500 mg, 2 x 450 mg rifampicin</td>
</tr>
<tr>
<td>03/2010</td>
<td>At follow-up visit three months after revision surgery the knee is still painful with intermittent effusions, no visible signs of implant loosening or infection</td>
</tr>
<tr>
<td>04/2010</td>
<td>Stop of antibiotic treatment</td>
</tr>
<tr>
<td>05/2010</td>
<td>Joint aspirate and periprosthetic tissue cultures were negative</td>
</tr>
<tr>
<td></td>
<td>Diagnosis: Postero-lateral impingement</td>
</tr>
<tr>
<td>07/2011</td>
<td>Arthrotomy with circumferential resection of hypertrophic synovialis</td>
</tr>
<tr>
<td></td>
<td>Antibiotic treatment: amoxicilin-clavulanic acid po 2 x 1 g</td>
</tr>
<tr>
<td>08/2011</td>
<td>08/2011 Patient presents for removal of suture material</td>
</tr>
<tr>
<td></td>
<td>persistent swelling of soft tissues, CRP 21 mg/l</td>
</tr>
<tr>
<td>Date</td>
<td>Event Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>09/2011</td>
<td>X-ray shows good position of prosthesis, no sign of loosening, CRP 25 mg/l</td>
</tr>
<tr>
<td>11/2011</td>
<td>After slight improvement antibiotic treatment was stopped despite persistent warmth of the knee, CRP 16 mg/l</td>
</tr>
<tr>
<td>12/2011</td>
<td>Persistent pain, difficulties in walking (needs two sticks!), function F/E: 30/0, swelling, warmth, free liquid, venous insufficiency, CRP 34 mg/l, ESR 18 mm/h; progressive implant loosening</td>
</tr>
<tr>
<td>01/2012</td>
<td>Important synovitis and free liquid; tremor left sided; F/E: 80/5; CRP 18 mg/l</td>
</tr>
<tr>
<td></td>
<td>Diagnosis: Most likely infection</td>
</tr>
<tr>
<td></td>
<td>Two weeks later removal knee prosthesis with synovectomy and monobloc spacer (local antibiotics in spacer 8 g gentamicin and 4 g vancomycin)</td>
</tr>
<tr>
<td></td>
<td>Swabs and tissue cultures still negative, histology and cell count indicate infection</td>
</tr>
<tr>
<td></td>
<td>Sonication of implant and culture of sonication fluid finally found a <em>Propionibacterium acnes</em> (too numerous to count)</td>
</tr>
<tr>
<td>02/2012</td>
<td>After 3 weeks implantation of the new knee prosthesis (local antibiotic in bone cement 1 g gentamicin and 1 g clindamycin) with systemic antibiotic treatment (amoxicillin and clavulanic acid 3 x 2.2 g iv for two weeks, rifampicin 2 x 450 mg po and 2 x 500 mg levofoxacin po for ten weeks)</td>
</tr>
<tr>
<td>04/2012</td>
<td>Back home, walks 1.5 km, light swelling, no redness, no warmth, no joint effusion; F/E 100/0; CRP 3 mg/l</td>
</tr>
<tr>
<td></td>
<td>still antibiotic treatment (levofloxacin + rifampicin)</td>
</tr>
<tr>
<td>06/2012</td>
<td>No pain; F/E 120/0; no swelling, no effusion; CRP &lt;2; antibiotics stopped</td>
</tr>
<tr>
<td>08/2012</td>
<td>End of treatment, patient cured</td>
</tr>
<tr>
<td>10/2013</td>
<td>Follow-up visit: no complaint</td>
</tr>
</tbody>
</table>
### Step 1: History

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
</thead>
</table>
| 2001  | Male, 60 years old  
Morbus Parkinson  
Severe osteoarthritis of right knee |
| 07/2008 | Primary Implantation of Total knee Prosthesis                                   |
| 09/2009 | Spondylodesis after transpedicular microdiscectomy L4/5                        |
| 11/2009 | Fever, Chills, CRP 123 mg/l (normal < 5 mg/l),  
Knee prosthesis: painful, no effusion  
Blood cultures: *Staphylococcus aureus* (MSSA) |
| 12/2009 | Removal of knee prosthesis and implantation of spacer with antibiotics  
(vancomycin 2 g/40 g PMMA)  
Antibiotic treatment: flucloxacillin 4 x 2 g iv 6 weeks |
| 01/2010 | Surgery: reimplantation at 6 weeks  
Antibiotic treatment: levofloxacin 2 x 500 mg, 2 x 450 mg rifampicin |
At follow-up visit three months after revision surgery the knee is still painful with intermittent effusions.

X-ray of right knee

**LEARNING POINTS**

*Detailed history is groundbreaking. Two to three years after surgery are the crucial time period for developing low grade PJI.*

*Based on clinical and experimental data, 100–1000 bacteria on the surface of the prosthesis are sufficient to cause PJI (cf. open fractures $10^4$ bacteria, soft tissue without implant $10^{6-8}$ bacteria).*

2.1 Biofilm and its biology. Why is PJI often so difficult to diagnose and treat?

**References**


Step 2: Clinical symptoms and physical examination

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/2010–03/2012</td>
<td>Persistent pain of the knee prosthesis</td>
</tr>
<tr>
<td>08/2011</td>
<td>Patient presents for removal of suture material</td>
</tr>
<tr>
<td>08/2011</td>
<td>Persistent swelling of soft tissues</td>
</tr>
</tbody>
</table>

What should be checked:

- Pain (Nature, Onset, Duration, Location)
- Wound discharge
- Joint swelling
- Range of motion
- Inspection and palpation (Deformity, Limb alignment, joint stability, gait, spine, adjacent joints evaluation)

Some signs like swelling and sinus are clear indications for infection (Definition of PJII). (2)
In case of low grade PJI often only pain is present. The pain is typically persistent or slowly increasing, starting immediately after primary or revision surgery or a few months later. Because of the chronic inflammation and progressive loosening of the implant, the pain usually increases over time. The physical examination helps to rule out other reasons for pain and/or implant failure.

**LEARNING POINT**

*In presence of a pain within the first years after implantation of a joint prosthesis low grade PJI should be considered until proven otherwise.*

2.2 The value of clinical diagnostics. Do clinical signs and symptoms support diagnosis of PJI?

References


Step 3: Imaging

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/2010</td>
<td>No visible signs of implant loosening or infection</td>
</tr>
<tr>
<td>09/2011</td>
<td>X-ray shows good position of prosthesis, no sign of loosening</td>
</tr>
</tbody>
</table>

Radiographs are not specific nor sensitive, but useful for follow-up observation. Aspects to be considered: implant loosening, bone density, induration, sequester, osteolysis, surrounding tissue reaction.
CT is more sensitive than radiography, especially for detection of sequester. MRI can be difficult to interpret because of implant artefacts. Radionuclide imaging (bone scan) has high sensitivity for inflammation, but the differentiation between septic and aseptic loosening is difficult. PET/CT gives little additional information. In low grade infection often no signs for loosening or infection are visible. Imaging Methods are mostly used to distinguish other causes for pain and failure of the implant.

LEARNING POINTS

Early implant loosening is a clear hint for low grade infection. In case of pain and no signs for implant loosening infection must be suspected too until proven otherwise. Some infections progress very slowly so the implant loosening is not yet visible at an early stage. (Definition of PJI).

In many cases differentiation between septic and aseptic loosening (aseptic failure) is difficult.

Conventional radiographs are sufficient as first imaging procedure. In complex situations other imaging techniques should be discussed.

2.3 The Value of Imaging. No radiological signs of infection – no PJI?

References

Step 4: Laboratory Diagnostics

**01/2010–03/2012**

Persistent elevated CRP between 20 and 30 mg/l

CRP curve of the patient during the whole diagnostic period

CRP:
Typically CRP level should drop to normal level (< 10 mg/l for CRP) after 3 weeks postoperative.
Deviations +/- 10 mg/l are within the biological range and don’t allow conclusions concerning the improvement process of the infection.
In PJI even CRP levels > 5 mg/l should be considered as signs for infection due to the biofilm.

**LEARNING POINTS**

No inflammatory marker has adequate sensitivity and specificity to approve or to exclude PJI.

In case of painful prosthesis or signs of early implant loosening (2–3 years postoperative) even normal laboratory markers are no criteria to exclude an infection.

It is important not only to look at the values of blood tests but at the dynamics of the value. While in acute infection are elevated and constantly rising in chronic infection levels can be within the normal range.

2.4 The value of laboratory diagnostics. What can laboratory blood tests tell us, if PJI is suspected?
Step 5: Preoperative microbiology and histopathology

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/2010</td>
<td>12 weeks after revision surgery stop of antibiotic treatment</td>
</tr>
<tr>
<td>05/2010</td>
<td>Joint aspirate and periprosthetic tissue cultures were negative</td>
</tr>
<tr>
<td></td>
<td>Diagnosis: Postero-lateral impingement</td>
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<tr>
<td></td>
<td>Arthrotomy with circumferential resection of hypertrophic synovialis</td>
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</tr>
<tr>
<td>09/2011</td>
<td>X-ray shows good position of prosthesis</td>
</tr>
<tr>
<td></td>
<td>No sign of loosening, CRP 25 mg/l</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="X-ray of right knee" /></td>
</tr>
<tr>
<td>11/2011</td>
<td>After slight improvement treatment was stopped despite persistent warmth of the knee, CRP 16 mg/l</td>
</tr>
</tbody>
</table>

Antibiotic treatment prior to the culturing can lead to false-negative cultures. They should be stopped at least two weeks before sampling. Be aware of difficult-to-detect bacteria (special microorganisms). For example, *P. acnes* may need up to 14 days until growth (bacterial culture incubation). Incubation of only seven day can have 26% false-negative cultures. But: longer incubation can lead to more contamination. So always complementary check other evidence for infection. Aerobic and anaerobic culturing is always necessary. For a high specificity and sensitivity of histological samples, an experienced histopathologist is needed. With joint aspiration/biopsy/tissue cultures you find planktonic bacteria, you cannot remove sessile bacteria, which live in a biofilm. Synovial fluid and periprosthetic tissue samples have a higher sensitivity and specificity than swabs.
<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>91.39</td>
<td>100</td>
<td>100</td>
<td>93.6</td>
<td>96.16</td>
</tr>
<tr>
<td>Periprosthetic tissue</td>
<td>78.94</td>
<td>80.95</td>
<td>78.95</td>
<td>80.95</td>
<td>80</td>
</tr>
<tr>
<td>Swab</td>
<td>80.65</td>
<td>99.5</td>
<td>98.68</td>
<td>88.68</td>
<td>91.91</td>
</tr>
<tr>
<td><strong>Chronic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>78.94</td>
<td>100</td>
<td>100</td>
<td>87.960</td>
<td>91.7</td>
</tr>
<tr>
<td>Periprosthetic tissue</td>
<td>56.98</td>
<td>80.95</td>
<td>67.12</td>
<td>73.38</td>
<td>71.23</td>
</tr>
<tr>
<td>Swab</td>
<td>39.53</td>
<td>99.29</td>
<td>97.14</td>
<td>73.06</td>
<td>76.75</td>
</tr>
</tbody>
</table>

Sensitivity, specificity, PPV and NPV of each sample according to the type of infection (acute or chronic) \(^3\)

It needs a team (surgeon and microbiologist) to get good results; correct sampling and correct testing are necessary. Be aware of the specifics of PJI (Biofilm).

- If only one of several samples is positive with low virulent organism in culture, this organism is considered contamination.
- Gram stain of periprosthetic tissue has low sensitivity.
- Enzyme strip test (leukocyte esterase) in synovial fluid was evaluated but the readings were often difficult to interpret.
LEARNING POINTS

Positive microbiology is not compulsory for diagnosing a PJI.

The number of required samples is based on the class of infection. If low grade infection is suspected, five or more samples are needed. In acute infections, three samples are sufficient.

Antibiotic treatment without knowing the microorganism should be avoided. Cultures become false-negative and even worse: resistance may be formed. In low grade infections only antibiotics active against biofilm are appropriate.

Always determine synovial-fluid leukocyte count. For knee PJI > 1700 Leukocytes/µl or > 65% neutrophil granulocytes and for hip PJI > 4200 Leukocytes/µl or > 80% neutrophil granulocytes are clear signs for infection. Add anticoagulants (EDTA, heparin) for determination of cell count (perform within 24 h) and differential, in case of high viscosity of the synovial-fluid add hyaluronidase. Remember that the cell count is not significant up to six weeks postoperative and for patients with rheumatic diseases or leukopenia.

Distribution of synovial fluid leukocyte count (A) and neutrophil percentage (B), by type of prosthetic knee arthroplasty failure. Dotted lines indicate proposed cutoff values to differentiate aseptic failure from prosthetic joint infection.
2.5 Correct preoperative sampling. How to perform joint fluid aspiration to guarantee best results

2.6 Preoperative diagnostics. What is the most important preoperative method for detecting PJI?

References


Step 6: Intraoperative microbiology and histopathology

12/2011 Persistent pain, difficulties in walking (needs two sticks!), function F/E: 30/0, swelling, warmth, free liquid, venous insufficiency, CRP 34 mg/l, ESR 18 mm/h; progressive implant loosening

X-ray of right knee, progressive implant loosening

01/2012 Important synovitis and free liquid; tremor left sided; F/E: 80/5; CRP 18 mg/l

Diagnosis: Most likely infection: two weeks later removal knee prosthesis with synovectomy and monobloc spacer (local antibiotics in spacer 8 g gentamicin and 4 g vancomycin)

Swabs and tissue cultures still negative but histology and cell count indicate infection

MRI of right knee showing free liquid
Preoperative joint aspiration and intraoperative tissue cultures represent the current gold standard (82% sensitivity and 98% specificity). New methods (sonication of the removed implant, molecular methods) have better sensitivity and will likely replace standard tissue cultures.

Gram stain has low sensitivity (only 20%) and should not be used to rule out PJI. Delay or inappropriate storage of specimen may lead to premature death or overgrowth of certain bacteria.

A valuable intraoperative quick test is the histopathological analysis (frozen section) of the periprosthetic membrane according to consensus-classification (93% Sensitivity). Intraoperative swabs should not be used because of low sensitivity and risk of contamination.

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**LEARNING POINTS**

*In case of loosening the implant can’t be retained. The removal of the prosthesis allows the detachment of adherent bacteria directly from the implant or the bone cement.*

*Remember that positive microbiology is not compulsory for diagnosing an infection. If there is one sign for infection (e.g. pain) the prosthesis must be considered infected until proven otherwise* (Definition). (2)

*Slow growing bacteria (e.g. P. acnes) need prolonged microbiological culturing for 2 weeks* (bacterial culture incubation). (1)

*An increase of diagnostic validity is given by the combined interpretation of sonication findings and histopathological consensus-classification (diagnostic methods).* (3)

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2.7 Correct intraoperative sampling. How to obtain significant results with intraoperative culture and histology

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**References**


Step 7: New methods

01/2012  Sonication of implant and culture of sonication fluid finally found a *Propionibacterium acnes* (to numberous to count)

02/2012  Implantation of the new knee prosthesis with local antibiotic prophylaxis (1 g gentamicin and 1 g clindamycin) and systemic antibiotic treatment (amoxicillin and clavulanic acid 3 x 2,2 g iv for two weeks, rifampicin 2 x 450 mg po and 2 x 500 mg levofloxacin po for ten weeks)

**Sonication** of implant and/or cement is actually the easiest, cheapest and most effective way to get the biofilm of the prosthesis for identification of the microorganisms. Besides culturing the sonication fluid can be used for additional investigations. Studies prove a sensitivity of 79% and a specificity of 99% for the diagnosis of PJI.

Culture plates. Left side: tissue biopsy, right side: sonication fluid. Sonication improves the detection of bacteria up to 10,000 times compared with periprosthetic tissue cultures

**Specific and multiplex Polimerase chain reaction (PCR)** are molecular methods. There are used in case of negative cultures (difficult to detect bacteria) and previous treatment with antibiotics. PCR doesn't give the susceptibility pattern of the strain (except methicillin-resistance).
Mass spectrometry (MALDI-TOF MS) is fast, reliable, easy-to-use, and cost-effective. Clinical samples or sonication fluid can be used directly. Like PCR the mass spectrometry doesn't give the susceptibility pattern of the strain. There are more innovative techniques (e.g. microcalorimetry, electrical method reverse transcription PCR, fluorescence in situ hybridization, biofilm microscopy, microarray identification, serological tests) under development that need to prove their sensitivity and specificity. Rapid, accurate and fully automatic diagnostic tests are supposed to be available soon. The new methods need to prove their reliability and are actually only used in case of negative cultures. For the long term it remains to be seen if new and innovative techniques will substitute culturing.
LEARNING POINT

In case of low grade infection there is no better diagnostic tool to identify the microorganisms than prosthesis sonication.

2.8 Sonication. How to improve intraoperative diagnostic yield for PJI

2.9 Intraoperative diagnostics. What are the most important intraoperative methods for identifying the microorganism

References


Step 8: Postoperative follow-up

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
</table>
| 04/2012 | Back home, walks 1.5 km, light swelling, no redness, no warmth, no joint effusion; F/E 100/0; CRP 3 mg/l  
Still antibiotic treatment (levofloxacin + rifampicin) |
| 06/2012 | No pain, F/E 120/0, no swelling, no effusion, CRP <2  
Antibiotics stopped |
| 08/2012 | End of treatment, patient cured |
| 10/2013 | Follow-up visit: no complaint |

CRP returns to normal after surgery after 1–2 weeks. While ESR can be elevated for months postoperative.
Summary low grade infection diagnosis

The diagnostic routine starts with detailed anamnesis and physical examination: risk factors and the interval to primary surgery give first hints on the type of the possible infection. In case of low grade infection there are often no clinical symptoms. Imaging techniques can't detect an infection but help you to find other reasons for pain. Nevertheless infection must be ruled out in case of implant loosening etc. Because of the slow growing bacteria low grade infections often show no signs of loosening or infection for a long time. Laboratory marker can be normal. CRP levels > 10 mg/l are signs for infection. In low grade cases even levels > 5 mg/l should be considered as signs for infection.

In preoperative diagnostic many microorganisms can’t be identified. But: Positive microbiology is not compulsory for diagnosing an infection. A synovial-fluid leukocyte count of > 2000 leukocytes/µl or > 70% neutrophils gives a clear hint for the diagnosis of an infection.

Important for histopathology and microbiology is the avoidance respectively the stop of antibiotic treatment prior to the testing and correct sampling (considering the microbiological specialities of biofilm microorganisms). No single laboratory test has perfect sensitivity and specificity for diagnosing infection. A combination of laboratory, histopathology, microbiology & imaging studies gives best results.

References

The best diagnostic tool is the prosthesis itself. The detachment of adherent bacteria is intraoperative possible via sonication of the implant. Attention should be paid to difficult to detect bacteria which need longer incubation time or even special diagnostic methods like PCR or mass spectrometry.

**LEARNING POINTS**

*Especially low grade infections can be very difficult to detect, for there might be hardly symptoms or suspicious findings. Often it’s a challenge to identify the microorganisms. But knowing the specifics of PJI (considering differences between low grade, haematogenous and early acute infection) the proper diagnostic steps will lead to successful outcome.*

*Remember: If there is only one indication PJI must be suspected and excluded.*

**Outlook: Some words on treatment**

Successful management of infection (including diagnosis) needs a team. PJI always requires a combination of surgery and antibiotic therapy. Treatment must be adapted to the individual clinical situation.
1.2 Learning case 2: acute haematogenous infection

Case summary: Male; 68 years old

In this learning case for many years the prosthesis was fine and suddenly there are signs of infection – time to act quickly. Even if detection of the microorganism seems to be relatively easy some diagnostic procedures should not be missed to eradicate the infection and avoid a chronic infection.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>Severe osteoarthritis of right knee</td>
</tr>
<tr>
<td>07/2008</td>
<td>Primary Implantation of Total knee Prosthesis</td>
</tr>
<tr>
<td>09/2011</td>
<td>Patient has problems with his knee prosthesis: knee prosthesis painful, warmth, joint effusion No visible signs of implant loosening or infection in x-ray Fever, chills, CRP 123 mg/l (normal &lt; 5 mg/l) Blood cultures: <em>Staphylococcus aureus</em> (MSSA) → Diagnosis: acute haematogenous infection without implant loosening</td>
</tr>
<tr>
<td>10/2011</td>
<td>Removal of knee prosthesis (3 weeks after the start of the symptoms) and implantation of spacer with antibiotics (vancomycin 2 g/40 g PMMA) Systemic antibiotic treatment (Flucloxacillin 4 x 2 g iv 6 weeks)</td>
</tr>
<tr>
<td>11/2011</td>
<td>Reimplantation at 6 weeks Antibiotik treatment (Levofloxacin 500 mg 2 x d; Rifampicin 450 mg 2 x d)</td>
</tr>
<tr>
<td>12/2011</td>
<td>4 weeks postoperativ: scar uneventful, function well, no pain, good mobility of the knee, CRP 5 Antibiotics stopped</td>
</tr>
<tr>
<td>03/2012</td>
<td>At follow-up visit three months after revision: no complaint</td>
</tr>
</tbody>
</table>
Step 1: History

2007  Male; 68 years old
       Rupture achilles tendon
       (OP 12/2007)

2008  Severe osteoarthritis of right knee

MRI of right knee

07/2008  Primary Implantation of Total knee Prosthesis

09/2011  Patient has problems with his knee prosthesis

Main risk factor for haematogenaous infection of orthopedic prosthesis is bacteraemia (Risk factors like rheumatoid arthritis, diabetes mellitus, obesity etc. are only relevant for exogenous caused infection). Joint prostheses are at risk for haematogenous infections due to production of synovial fluid and potential filtration of bacteria into the joint space. In case of bacteraemia approx. 50% of all knee prosthesis, approx. 30% hip prosthesis, approx. 20% shoulder, elbow and ankle joint prosthesis get infected.\(^1\) Haematogenous infections are caused endogeneously mostly by skin inflammation, lunge inflammation, urinary tract infection, intestinal infection or tooth infection. In about 30% no primary focus can be identified (primary bacteraemia).\(^2\)

If a prosthesis gets infected more than two years after surgery it can be classified as haematogenous infection (Classification). Exogenous infections only occur within the first two years after surgery (Pathogenesis).
Exogenous = acquired during surgery / intervention; early infection: 30%; delayed ("low-grade") infection: 30%.
Endogenous = inoculation either by remote seeding from distant infection focus through blood stream (haematogenous infection: 30%) or by local spread (per continuitatem) from adjacent infection focus, e.g. skin infection (contiguous infection: 10%).
After osteosynthesis there is no higher risk of haematogenous infection.

LEARNING POINT

*The risk of haematogenous infection exists throughout life and is cumulating over the years (0,25% per year/prosthesis).*
2.1 Biofilm and its biology. Why is PJI often so difficult to diagnose and treat?

References

Step 2: Clinical symptoms and physical examination

09/2011

Systemic symptoms:
- fever, chills

Local symptoms: knee prosthesis painful, warmth, joint effusion

Pain curve of the patient ascertained with a visual analog scale (VAS) for rating pain from 0 (no pain) to 10 (worst possible pain) covering the whole diagnostic period from beginning of bacteraemia to end of treatment.

What should be checked:
- Pain (Nature, Onset, Duration, Location)
- Wound discharge or other wound problems
- Joint swelling
- Range of motion
- Inspection and palpation (Deformity, Limb alignment, joint stability, gait, spine, adjacent joints evaluation)

Some signs like swelling and sinus are clear indications for infection (Definition of PJI). The physical examination helps to rule out other reasons for pain and/or implant failure (Aseptic causes of implant failure).

LEARNING POINTS

In haematogenous infections local signs of prosthetic joint infection may present after several days. Therefore daily targeted examination of all joints, especially prosthetic joints is important.

It is important to act fast if there is pain, swelling, redness etc. The retention of the prosthesis is only possible within the first 3 weeks after the start of symptoms (Treatment algorithm).

2.2 The value of clinical diagnostics. Do clinical signs and symptoms support diagnosis of PJI?
References


Step 3: Imaging

09/2011  No visible signs of implant loosening or infection in x-ray

X-ray of right knee

X-ray is used to rule out other possible reasons for problems with the prosthesis e.g. periprosthetic fractures, loosenings. In haematogenous infections due to the rapid progress of the infection there are often not yet signs for loosening. (Radiological studies).

A CT scan of the whole body is useful to identify the focus of inflammation.

LEARNING POINT

If a patient has more than one joint prosthesis it is important to check all of them accurately using scintigraphy, PET or joint aspiration.

2.3 The Value of Imaging. No radiological signs of infection – no PJI?
Step 4: Laboratory diagnostics

<table>
<thead>
<tr>
<th>Date</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/2011</td>
<td>CRP 123 mg/l (normal &lt; 5 mg/l)</td>
<td><img src="image" alt="CRP Curve" /></td>
</tr>
</tbody>
</table>

A high CRP level (between 50 and 400 mg/l) is typical in case of haematogenous infection. *(Diagnostic algorithm).*

Due to the bacteraemia not only CRP levels but all biomarker are elevated.

**LEARNING POINT**

*Should CRP/biomarker levels do not steadily decrease after operation other infectious foci should be excluded (septic thrombosis, endocarditis, other bone or joint infection, e.g. vertebral osteomyelitis).*

2.4 The value of laboratory diagnostics. What can laboratory blood tests tell us, if PJI is suspected?

Step 5: Preoperative microbiology and histopathology

<table>
<thead>
<tr>
<th>Date</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/2011</td>
<td>Blood cultures: <em>Staphylococcus aureus</em> (MSSA)</td>
</tr>
<tr>
<td></td>
<td>Diagnosis: acute haematogenous infection without implant loosening</td>
</tr>
</tbody>
</table>

As the number of leukocytes is always high when there is an infection leukocyt count and differential of synovial fluid are not used to diagnose infection in haematogenous cases (different from delayed low grade infection, where
leukocyte count in synovial fluid is the most important preoperative diagnostic method). But it is helps rule out an infection of the joint: if the leukocyte count in synovial fluid lies within the normal range a joint infection can be excluded. (Cut offs: leukocytes: $> 1.7 \times 10^9$; neutrophils $> 65$%; please note: cut offs differ from early postoperative infections).

<table>
<thead>
<tr>
<th></th>
<th>Native joints</th>
<th>Prosthetic joints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Septic Arthritis</td>
</tr>
<tr>
<td>Leukocytes, x 10^9/l</td>
<td>&lt;0.2</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>&lt;25</td>
<td>&gt;90</td>
</tr>
</tbody>
</table>

Cell counts in synovial fluid of patients with native and prosthetic joints (Excluded: early postoperative phase (3 months) and inflammatory joint diseases)\(^{(1)}\)

Before antibiotic treatment is started it is important to take at least blood cultures, which often give good results. In addition it is useful to aspirate the synovial fluid for microbiological culturing, because blood cultures are not always positive. Synovial fluid cultures are usually positive in case of infection (the more pus the more difficult it is to find microorganisms).

If the antibiotic treatment has been started before sampling it is useful to use new diagnostic methods, especially PCR of the synovial fluid. PCR finds microorganisms killed by antibiotics too and gives fast results within a few hours.

The higher the number of microorganisms causing bactaeremia, the higher is the risk of getting the prosthesis infected (and the short the time to detect the microorganisms in blood cultures).
LEARNING POINTS

*Haematogenous infections are mostly monobacterial (spectrum of microorganisms).*

*If PJI is not clear a puncture should always be performed to diagnose the infection and isolate the causing microorganism.*

*It is important to start the treatment fast so the infection cannot spread to other joints, regions or organs. But remember to take at least blood cultures before starting the antibiotic therapy.*

*Haematogenous PJI can become chronic if antibiotics are administered empirically (without knowing the microorganism) and if not combined with surgical treatment. Aggravation by neglect can lead to chronic PJI too.*

*In rare cases cultures are negative, especially of samples after start of antibiotic treatment: then gram stain from sonication fluid (50% sensitivity) and PCR can detect the microorganisms.*

2.5 Correct preoperative sampling. How to perform joint fluid aspiration to guarantee best results

2.6 Preoperative diagnostics. What is the most important preoperative method for detecting PJI?

References

Step 6: Intraoperative microbiology and histopathology

10/2011
3 weeks after the start of the symptoms) Removal of knee prosthesis and implantation of spacer with antibiotics (vancomycin 2 g/40 g PMMA)

Systemic antibiotic treatment (Flucloxacillin 4 x 2 g iv 6 weeks)

Retention of the prosthesis is possible in case of haematogenous infection if symptoms started less than 3 weeks ago. Then no one- or two-stage exchange is needed but a debridement, change of mobile parts is performed. If the prosthesis is exchanged short-interval with local antibiotics in the spacer can be performed. (Treatment algorithm).

Normally the microorganism can be identified preoperative. Intraoperative diagnostics then serves as confirmation of the preoperative findings and improves targeted antibiotic therapy. That is why microbiological culturing of intraoperative tissue samples as well as sonication fluid from sonication of the mobile parts of the prosthesis should be performed additionally. In acute (early postoperative as well as haematogenous) infections usually all tissue and sonication fluid samples are positive if harvested before start of antibiotic treatment. If you use sonication the microorganisms grow faster and no prolonged incubation time is needed (1). As basis for PCR sonication fluid can provide fast results.

LEARNING POINTS

The goal for the diagnosis and treatment of haematogenaous infections should be the retention of the prosthesis if possibel. If one debridement is insufficient (approx. 20%) a second debridement is needed again accompanied by the change of all mobile parts.

Intraoperative diagnostic methods (tissue biopsy and implant sonication) should be used to verify the diagnosis and facilitate a targeted antibiotic therapy. (Intraoperative diagnostics)

2.7 Correct intraoperative sampling. How to obtain significant results with intraoperative culture and histology

2.8 Sonication. How to improve intraoperative diagnostic yield for PJI

2.9 Intraoperative diagnostics. What are the most important intraoperative methods for identifying the microorganism
Step 7: Postoperative follow-up

11/2011  Reimplantation at six weeks, ongoing AB therapy (Levofloxacin 500 mg 2 x d; Rifampicin 450 mg 2 x d)

12/2011  4 weeks postoperativ: scar uneventful, function well, no pain, good mobility of the knee, CRP 5

03/2012  At follow-up visit three months later: no complaint

CRP returns to normal after surgery after 1–2 weeks (see diagram below). While ESR can be elevated for months postoperative.

ESR and CRP levels after hip and knee arthroplasty

References

Summary acute haematogenous infection diagnosis

If there is an infection with fever or chills, it is important to check prosthetic joints, even if there are not jet any clinical signs (like pain). Haematogenous infections at prosthetic joints can be easily overlooked as clinical signs are often not distinct. Due to the rapid progress of the infection there are often not yet signs for loosening. Within the first two years after surgery the risk of haematogenous infection is highest (0,5% per year/prosthesis, from the third year on 0,25% per year/prosthesis) but the risk of haematogenous infection exists throughout life and is cumulating over the years. Having a bloodstream infections (BSI) the port of entry (e.g. intravascular catheter), the affected joint and the way between, e.g. cardiac pace maker, heart valve, or vascular graft have to be checked. If a patient has more than one joint prosthesis it is important to check all of them accurately using scintigraphy, PET or joint aspiration. Have a look at the native joints too.
It is important to act fast if there is pain, swelling, redness etc. The retention of the prosthesis is only possible within the first 3 weeks after the start of symptoms. Remember to take at least blood cultures before starting the antibiotic therapy. Haematogenous PJI can become chronic if antibiotics are administered empirically (without knowing the microorganism) and if not combined with surgical treatment. Aggravation by neglect can lead to chronic PJI too. In rare cases cultures are negative: then gram stain from sonication fluid (50% sensitivity) and PCR can detect the microorganisms. Anyway intraoperative diagnostic methods (tissue biopsy and implant sonication) should be used to verify the diagnosis and facilitate a targeted antibiotic therapy.

Outlook: Some words on treatment

Successful management of infection (including diagnosis) needs a team. PJI always requires a combination of surgery and antibiotic therapy. Treatment must be adapted to the individual clinical situation (Treatment algorithm). In case of haematogenous infections it is important to act fast and avoid the spread of the infection.
1.3 Learning case 3: early postoperative infection

Case summary: Male; 75 years old

In this learning case problems occur shortly after surgery. Then it is important to act fast to eradicate the infection before maturation of biofilm to avoid a chronic infection.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/2004</td>
<td>Psoriasis (with skin changes on the trunk), treated with low dose steroids since 2011, chronic renal insufficiency</td>
</tr>
<tr>
<td>07/2014</td>
<td>Primary implantation of total hip prostheses left and right hip</td>
</tr>
<tr>
<td>01.11.2014</td>
<td>Increasing pain in right hip since 1 year</td>
</tr>
<tr>
<td></td>
<td>Preoperative joint aspiration (3 months before revision)</td>
</tr>
<tr>
<td></td>
<td>Synovial fluid: 300/µl leukocytes, 25% granulocytes</td>
</tr>
<tr>
<td>01.11.2014</td>
<td>Hip prosthesis one-stage exchange for aseptic loosening, uncemented</td>
</tr>
<tr>
<td></td>
<td>Perioperative prophylaxis with a single dose cefazolin 2 g i.v. 30 min before incision</td>
</tr>
<tr>
<td>03.11.2014</td>
<td>Persistent wound secretion after surgery</td>
</tr>
<tr>
<td>05.11.2014</td>
<td>CRP 155 mg/l (day 3 postoperative)</td>
</tr>
<tr>
<td>08.11.2014</td>
<td>CRP 115 mg/l (day 5 postoperative)</td>
</tr>
<tr>
<td>08.11.2014</td>
<td>CRP 140 mg/l (day 8 postoperative)</td>
</tr>
<tr>
<td>09.11.2014</td>
<td>Fever 38.9 °C, no chills (day 9 postoperative)</td>
</tr>
<tr>
<td></td>
<td>No sings of fracture or dislocation</td>
</tr>
<tr>
<td></td>
<td>In blood cultures (2 pairs) <em>Staphylococcus aureus</em> (Methicillin-susceptible, MSSA) after 24 hours of incubation</td>
</tr>
<tr>
<td></td>
<td>Diagnosis: early postoperative infection</td>
</tr>
</tbody>
</table>
10.11.2014  CRP 180 mg/l (day 10 postoperative)
Revision surgery: debridement, change of mobile parts, removal of hematoma/fibrinous
Collection of 5 tissue samples for microbiology and mobile parts of the prosthesis for sonication (femur head and polyethylen inlay)
Antibiotic treatment: Flucloxacillin (4 x 2 g i.v.) + Rifampicin (2 x 450 mg p.o.) for two weeks
Culture results: *Staphylococcus aureus* (Methicillin-susceptible, MSSA) >1000 CFU/ml of sonication fluid and in 5/5 tissue samples (culture growth on the following day)

13.11.2014  Drainages removed on day 3 after second (septic) revision, wound remained without discharge

20.11.2014  Patient discharged 10 days after second revision, fully mobilized
Antibiotic treatment after two weeks: Levofloxacin (2 x 500 mg p.o.) + Rifampicin (2 x 450 mg p.o.)

Step 1: History

Male, 75 years old
Psoriasis (with skin changes on the trunk), treated with low dose steroids since 2011, chronic renal insufficiency

11/2004  Primary implantation of total hip prostheses left and right hip

07/2014  Increasing pain in right hip since 1 year
Preoperative joint aspiration 3 months before revision (synovial fluid: 300/µl leukocytes, 25% granulocytes)

X-ray of loosened hip right
Early postoperative infections are typically (but not only) caused exogenously. Risk factors apart from the condition of the patient (Risk factors like rheumatoid arthritis, diabetes mellitus, obesity, psoriasis, etc.) are hygiene in the operating theatre and duration of surgery. (Risk factors)

Exogenous infections are acquired during surgery / intervention (early infection: 30%; delayed, “low-grade” infection: 30%). Endogenous inoculate either by remote seeding from distant infection focus through blood stream (haematogenous infection: 30%) or by local spread (per continuitatem) from adjacent infection focus, e.g. skin infection (contiguous infection: 10%).

Due to modern surgery techniques and an improved standard of hygiene the risk for early postoperative infections after primary joint replacement could be reduced to 1% and after revision surgery to 4–6% (Epidemiology).
LEARNING POINTS

If a prosthesis gets infected up to 4 weeks after surgery it can be classified as early postoperative infection (Classification), but remember: Endogenous infections can occur anytime (Pathogenesis).

After primary or revision surgery it is important to regularly check if there are signs for PJI.

References


Step 2: Clinical symptoms and physical examination

Local symptoms:
persistent wound secretion after surgery (01.11.2014)

Persistent wound secretion (1)

08.11.2014

Purulent discharge from the incision wound, redness, swelling and increasing pain at surgical site (day 8 postoperative)

Pain curve of the patient ascertained with a visual analogue scale (VaS) for rating pain from 0 (no pain) to 10 (worst possible pain) covering the whole diagnostic period from implantation to end of treatment.
Early postoperative infections are mostly caused by highly virulent microorganisms such as *S. aureus* or gram-negative bacilli. Clinical signs of infection present early after implantation (Classification). Early infections typically manifest as local signs such as acute onset of joint pain, soft tissue swelling, joint effusion, erythema and warmth at the implant site. Sometimes systemic symptoms like fever and chills are present (Definition of PJI).

In addition, fever after surgery may indicate a surgical site infection.

What should be checked:
- Pain (nature, onset, duration, location)
- Wound discharge or other wound healing problems
- Soft tissue swelling, warmth and redness
- Range of motion
- Inspection and palpation (deformity, limb alignment, joint stability, gait, spine, adjacent joints evaluation)

Purulent wound discharge

Early postoperative infection can go along with partly fulminant aggravation of both the function of the prosthesis and medical condition of the patient.
LEARNING POINTS

In early postoperative infections local signs of prosthetic joint infection may present several days or weeks after surgery (up to 4 weeks). Therefore daily targeted examination of the soft tissues at surgical site is important.

The more aggressive the microorganism the earlier and more prominent are the symptoms; and the easier the diagnosis.

Postoperative complications such as wound healing problems or haematoma must be actively ruled out. Patients need to be educated to report any aggravation immediately.

If wound discharge continues beyond 5–7 days after surgery (risk for secondary infection from outside) or reappears within 4 weeks after surgery infection should be suspected. Imminent surgical revision with exchange of mobile parts is strongly considered.

In case that PJI is suspected (if there is pain, swelling, redness etc.) it is important to act fast. The retention of the prosthesis is only possible within the first 4 weeks after surgery (Treatment algorithm).

---

2.2 The value of clinical diagnostics. Do clinical signs and symptoms support diagnosis of PJI?

References


Step 3: Imaging

No signs of fracture or dislocation

X-ray of right hip

X-ray is used to rule out other possible reasons for problems with the prosthesis e.g. periprosthetic fractures or dislocations. In early postoperative infection due to the rapid progress there are often not yet signs for loosening. (Radiological studies) \(^{(1)}\)

As optional investigation ultrasound of the joint can be performed to detect joint effusion.

LEARNING POINT

*Imaging is of little relevance in case of early postoperative infection. There are often clear clinical signs.*

2.3 The Value of Imaging. No radiological signs of infection – no PJI?

References

Step 4: Laboratory diagnostics

CRP (normal < 5 mg/l):

<table>
<thead>
<tr>
<th>Date</th>
<th>CRP Value (mg/l)</th>
<th>Postoperative Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>03.11.2014</td>
<td>155</td>
<td>3</td>
</tr>
<tr>
<td>05.11.2014</td>
<td>115</td>
<td>5</td>
</tr>
<tr>
<td>08.11.2014</td>
<td>140</td>
<td>8</td>
</tr>
<tr>
<td>10.11.2014</td>
<td>180</td>
<td>10</td>
</tr>
</tbody>
</table>

CRP is a non specific biomarker which can be elevated because of wound healing after intervention or any infection including but not only surgical site infection. CRP returns to normal after 1–2 weeks postoperative.

Procalcitonin brings no additional information to CRP. ESR can be elevated for months postoperative and is therefore less appropriate for diagnosing early postoperative PJI.

A serial determination of CRP is needed to evaluate a possible postoperative infection.

**LEARNING POINT**

*Should CRP level do not steadily decrease after surgery infection must be suspected. It is better to check biomarkers regularly for follow-up. Repeated controls give more information than one single value.*

2.4 The value of laboratory diagnostics. What can laboratory blood tests tell us, if PJIs is suspected?
Step 5: Preoperative microbiology and histopathology

09.11.2014

In blood cultures (2 pairs) *Staphylococcus aureus* (Methicillin-susceptible, MSSA) after 24 hours of incubation

*Staphylococcus aureus* colonies on blood agar

In case of fever or chills two pairs of blood culture bottles (aerobic and anaerobic) should be collected. Acute postoperative infections spread only in 30%. If there is no fever, most likely no pathogens can be found in the blood.

Aerobic and anaerobic blood culture bottles

The number of leukocytes is always high after surgery. Leukocyte count and differential of synovial fluid are not used to diagnose infection in early postoperative cases (different from delayed low grade infection, where leukocyte count in synovial fluid is the most important preoperative diagnostic method). Remember that the cell count is not significant up to 6 weeks postoperative and for patients with rheumatic diseases or leukopenia. In early postoperative infection joint aspiration is not a relevant diagnostic option. Time is running. First, the infection may spread. So there is no time...
to waist while waiting for growth. Secondly, implant retention is only possible within 3 weeks time after onset of the symptoms. Thirdly, every additional intervention bears the risk of (further) contamination. Due to clinical symptoms surgical debridement with exchange of mobile parts is strongly considered even if no microorganism is detected preoperatively.

**LEARNING POINTS**

*It is important to start surgical treatment fast so the infection cannot spread and retention of the prosthesis is possible before the formation of biofilm occurs.*

*Antibiotic treatment should not be administered before collection of samples (except in septic patients).*

*Early postoperative PJI can become chronic if antibiotics are administered empirically (without knowing the microorganism) and without surgical intervention. Aggravation by neglect can lead to chronic PJI too.*

---

2.5 Correct preoperative sampling. How to perform joint fluid aspiration to guarantee best results

2.6 Preoperative diagnostics. What is the most important preoperative method for detecting PJI?

**References**


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**Step 6: Intraoperative microbiology and histopathology**

**10.11.2014**

Surgery (day 10 postoperative)

Revision surgery: debridement, change of mobile parts, removal of hematoma/fibrinous

Collection of 5 tissue samples for microbiology and mobile parts of the prosthesis for sonication (femur head and polyethylene inlay)

Antibiotic treatment: Flucloxacillin (4 x 2 g i.v.) + Rifampicin (2 x 450 mg p.o.) for two weeks
Culture results: *Staphylococcus aureus* (Methicillin-susceptible, MSSA) >1000 CFU/ml of sonication fluid and in 5/5 tissue samples (culture growth on the following day)

In early postoperative infections normally the microorganism can be identified via blood culture or intraoperative diagnostics. Once the pathogen is identified empiric treatment is de-escalated to targeted antibiotic therapy.

Even if the microorganism is identified preoperatively microbiological culturing of intraoperative tissue samples as well as sonication fluid from sonication of the mobile parts of the prosthesis should be performed additionally. In acute (early postoperative as well as haematogenous) infections usually all tissue and sonication fluid samples are positive if harvested before start of antibiotic treatment.

Intraoperative sampling and culturing is essential for targeted systemic antibiotic therapy if no microorganism is detected preoperatively.

The use of sonication of the mobile parts of the prosthesis improves results: the microorganisms grow faster and no prolonged incubation time is needed\(^1\). PCR of the sonication fluid can provide fast results within a few hours.

**LEARNING POINTS**

*During surgery multiple (at least three) intraoperative tissue specimen should be collected and the removed mobile parts of the prosthesis should be sent for sonication to confirm the suspected infection. Intraoperative diagnostic methods (tissue biopsy and implant sonication) should be used to verify the diagnosis and facilitate a targeted antibiotic therapy. (Intra-operative diagnostics)\(^2\)*

*Antibiotic treatment should not be administered before collection of samples (except in septic patients).*

*The goal for the diagnosis and treatment of early postoperative infections should be the retention of the prosthesis if possible.*

*Retention of the prosthesis is possible in case of early postoperative infection if surgery was less than 4 weeks ago.\(^3\) Then a surgical debridement and exchange of mobile parts of the prosthesis is performed.*

2.7 Correct intraoperative sampling. How to obtain significant results with intraoperative culture and histology
2.8 Sonication. How to improve intraoperative diagnostic yield for PJI

2.9 Intraoperative diagnostics. What are the most important intraoperative methods for identifying the microorganism

References


Step 7: Postoperative follow-up

13.11.2014 Drainages removed on day 3 after second (septic) revision, wound remained without discharge

20.11.2014 Patient discharged 10 days after second revision, fully mobilized

Antibiotic treatment after two weeks: Levofloxacin (2 x 500 mg p.o.) + Rifampicin (2 x 450 mg p.o.)

CRP returns to normal after surgery during 1–2 weeks while ESR can be elevated for months postoperative.

ESR and CRP levels after hip and knee arthroplasty (1)
Check CRP and clinical symptoms regularly to make sure that the infection is eradicated. If one debridement is insufficient (approx. 20%) a second debridement is needed again accompanied by the change of all mobile parts. In rare cases (approx. 5%) a third debridement and change of all mobile parts is necessary. Again the maturation for biofilm is crucial for prosthesis retention so all procedures must be within the time frame of max. 3 weeks after the first symptoms.

References


Summary early postoperative infection diagnosis

Early postoperative infections are typically manifested as an acute onset of fever, joint pain, effusion, erythema and warmth at the implant site, and are commonly caused by virulent microorganisms, such as *Staphylococcus aureus* and gram-negative bacilli. Due to the rapid progress of the infection there are often not yet signs for implant loosening. If wound discharge continues or reappears beyond 7 days after surgery infection should be suspected and surgical debridement with exchange of mobile parts is strongly considered. It is important to act fast. The retention of the prosthesis is only possible within the first four weeks after the surgery. The goal for the diagnosis and treatment of early postoperative infections should be the retention of the prosthesis if possible. So it is important to act fast. Preoperative joint aspiration for leukocyte count and culture is not a relevant diagnostic option. Intraoperative diagnostic methods (tissue biopsy and implant sonication) should be used to verify the diagnosis based on clinical signs and facilitate a targeted antibiotic therapy.

Outlook: Some words on treatment

Successful management of infection (including diagnosis) needs a team. PJI always requires a combination of surgery and antibiotic therapy. Treatment must be adapted to the individual clinical situation. (Treatment algorithm) In case of early postoperative infection it is important to act fast and avoid the spread of the infection. Within the first four weeks after surgery a retention of the prosthesis is possible.
2. CHALLENGES IN PJI DIAGNOSIS

The challenges section is offering detailed knowledge including practical tips and videos around infection diagnosis. The most frequent questions and problems related to PJI diagnosis are presented and discussed. What is the role of Biofilm in PJI? How should joint aspiration be performed to avoid contamination and detect the causative microorganism? What are the most important preoperative diagnostic methods for detecting PJI? What is sonication and does it improve results? You learn how to improve sensitivity by correct sample taking, which laboratory blood test gives best results and much more. The differences between early, delayed and haematogenous infections are taken into consideration to help you understand the speciality of every infection type.

If your e-reader is not able to open the educational videos please visit http://www.heraeus-palacademy.com where you can find these and other videos.
2.1 Biofilm and its biology. Why is PJI often so difficult to diagnose and treat?

Microorganisms associated with PJI causing implant loosening are found attached to the prosthesis where they often form a biofilm, one of the most resistant forms of life\(^1,2\). Biofilms render PJI difficult to diagnose and to eradicate. In particular, low-grade infection is difficult to distinguish from aseptic failure. It is crucial, however, to identify cases with septic loosening due to biofilm-associated infection because this has therapeutic implications. For example, non-infectious implant loosening can be treated by 1-stage exchange whereas delayed low-grade infection usually requires a 2-stage approach\(^3\).

The protective nature of biofilm

In contrast to their free-living planktonic counterparts microorganisms in biofilms live clustered together in a highly hydrated extracellular matrix ("slime") attached to a surface.

- Depletion of metabolic substances or waste product accumulation causes these "sticky" microbes to enter a **slow- or non-growing stationary (sessile) state**\(^4,5\).
- Within biofilms, bacterial cells develop into **organized and complex communities** resembling multicellular organisms\(^6\). Release of cell-to-cell signaling molecules (quorum sensing) induces bacteria in a population to respond in concert by changing patterns of gene expression involved in biofilm differentiation\(^7\).
- Proximity of cells within the microcolony provides an ideal environment for the **exchange of genes** located on extrachromosomal DNA (plasmids).

A biofilm therefore represents a basic survival mechanism by which microbes resist external and internal environmental factors, such as antibiotics and the host immune system\(^8\). Biofilm microorganisms are up to 1,000 times more resistant to growth-dependent antimicrobial agents than planktonic microorganisms\(^4,5\).

Biofilm develops rapidly

Development of biofilm is a fast process which usually takes minutes to hours to complete. In this process already less than 100 colony-forming bacteria can cause an infection\(^9\). In acute infection the implant can usually only be
rescued within approx. 3 weeks after the onset of symptoms (3), because the development of biofilm remains limited to the surface of the implant. In general, subsequent extension of the biofilm to the bone after about 3 weeks results in implant loosening. The problem for diagnosis is the fact that biofilm can only be diagnosed when it starts to release bacteria to the surrounding regions.

Biofilm development:
1) and 2) Adhesion to the surface of an implant usually occurs within minutes
3) After 2–3 hours bacteria start to proliferate, form layers and adhere more firmly on the surface
4) Within 24 hours a stable biofilm has developed
5) Now bacteria can leave the biofilm and colonize other regions (10–12)
LEARNING POINTS

Biofilm biology requires your special consideration:

Extend the culture time of any microbiological sample to 10–15 days due to reduced bacterial growth in the biofilm.

Because of the sessile form bacteria often can't be found in tissue samples or synovial fluid. Consider sonication of the explanted prosthesis (or mobile parts of the prosthesis) in case of revision surgery to improve sensitivity of the culture of samples (13, 14).

Due to reduced bacterial growth implant loosening may be delayed and can be radiological visible only after three or more months.

Only early biofilms are possible to eradicate with antibiotics, an infected implant with formed mature biofilm is not possible to retain. As PJI always requires a combination of surgery and antibiotic therapy debridement and change of mobile parts of the prosthesis must be performed.

For cure of an implant-associated infection antimicrobial treatment needs to be active against biofilms.

For the diagnosis (and treatment) of a low-grade infection with biofilm teamwork between surgeon, microbiologist and infectiologist is crucial.

References


2.2 The value of clinical diagnostics. Do clinical signs and symptoms support diagnosis of PJI?

Clinical history and physical examination form an integral part of the diagnostic process. A high index of clinical suspicion for infection is the starting point of further diagnostic workup.

In general, PJI should be clinically suspected in case of persistent, remitting or increasing joint pain. Other clinical indicators are delayed wound healing, a recent invasive procedure, immunosuppression, joint effusion and suspicious radiological and laboratory diagnostic tests \(^{(1)}\).

By definition, diagnosis of infection is proven if a sinus tract is present and in case of visible purulence from wound discharge or an abscess. For the different types of infection (acute and chronic) there are differences in signs and symptoms.

**Acute PJI**

Hallmarks of acute infection include persistent local pain, erythema, hyperthermia, swelling, edema, wound dehiscence and secretion. In early acute infection (i.e., ≤ 4 weeks after implantation) inflammatory signs such as fever, sepsis syndrome, elevated inflammatory serum markers or an elevated neutrophil count may be missing \(^{(2)}\). The differential diagnosis of early acute PJI therefore includes wound complications such as hematoma or seroma. In early acute infection, revision of the wound is required to establish the diagnosis \(^{(3)}\). Intraoperative microbiological sampling and sonication of the removed mobile parts of the prosthesis are important to verify the diagnosis and enable a targeted antibiotic therapy.
Early infection with a persistently exuding wound that has been symptomatic for 15 days (4)

In acute PJI emerging beyond the postoperative period (i.e., > 3 months after implantation) systemic signs of inflammation are prominent, whereas soft tissue damage is less pronounced than in early PJI (2).

Chronic PJI

In delayed low-grade and late chronic PJI significant clinical signs and symptoms are often missing or therefore are not sufficient for an accurate diagnosis (3). Constitutional symptoms like persistent pain (with or without a period free of complaint after surgery) are typical. Hence, a combination of further tests is mandatory, such as analysis of the aspiration fluid, in particular synovial fluid leukocyte count and differential as well as inflammation marker testing and imaging.
**LEARNING POINTS**

*Consider any painful joint replacement to be infected until proven otherwise.*

*In acute infections there are often clear clinical signs which prove diagnosis of infection.*

*Remember that a patient may have low-grade or chronic infection with no or only minor clinical signs of infection.*

*Chronic PJI is almost never complicated by a sepsis syndrome. Therefore, you have sufficient time for a thorough diagnostic workup.*

*Especially in low-grade or chronic PJI further measures are needed for diagnosis, in particular a synovial fluid leukocyte count and differential of the aspiration fluid.*
References


2.3 The value of imaging. No radiological signs of infection – no PJI?

Imaging techniques for PJI can include conventional radiography, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and a radionuclide scan (bone scintigraphy, PET-CT). These studies may support the diagnosis of PJI, but the absence of radiological signs does not exclude the presence of infection.

**Value of different radiological techniques**

**Plain radiography** is neither specific nor sensitive. However, rapid development of a continuous translucent line of greater than 2 mm or severe focal osteolysis within the first year is often associated with infection. Examination of serial radiographs after implantation is helpful, but is neither sensitive nor specific enough to diagnose infection\(^{(1, 2)}\).

**CT and MRI** are more sensitive than plain radiography in the imaging of joint space. MRI is superior to CT and radiography in soft tissue resolution. The main limitation of both techniques is the presence of a (in general non-magnetic) metal implant that can result in image artefacts.

**Ultrasound** helps to detect periprosthetic fluid effusions and is especially useful in the infected total hip replacement to evaluate abscess collection.

**Bone scintigraphy** with technetium-99 is very sensitive to detect inflammation, but has a low specificity for diagnosing PJI\(^{(3, 4)}\). In addition, increased early bone remodelling around the prosthesis and aseptic loosening cannot be differentiated from infection.
LEARNING POINTS

Radiological signs of implant loosening cannot be detected until 3 months after infection.

Remember that the absence of radiological signs does not exclude the absence of infection.

A combination of different diagnostic studies is usually required to diagnose PJI. A negative bone scintigraphy scan excludes infection with high probability due to its excellent sensitivity, but a positive result requires further testing.

No imaging methods can differentiate between septic and aseptic cases. Most of the time imaging is used to rule out other reasons for problems with the prosthesis (e.g. periprosthetic fractures or dislocation).

References

2.4 The value of laboratory diagnostics. What can a laboratory blood test tell us if PJI is suspected?

Routine blood tests for the diagnosis of PJI may include white blood cell count (WBC), the determination of conventional markers of inflammation such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as well as determination of newer inflammatory markers such as procalcitonin (PCT) and interleukin-6 (IL-6) \(^{(1)}\).

**What blood test should I prefer?**

Determination of CRP appears to be the clinically most relevant of the current inflammatory marker tests. Even tough CRP is a non specific biomarker which can be elevated because of wound healing after intervention o any infection including but not only surgical site infection CRP values have been shown to distinguish between patients with and without PJI. In contrast, ESR is rather unspecific and PCT is not sensitive enough for local joint infection and does not allow to distinguish patients with infection from controls or patients without infection \(^{(4)}\).
### Characteristics of laboratory blood tests for diagnosis of PJI

<table>
<thead>
<tr>
<th>Blood marker</th>
<th>Comment</th>
</tr>
</thead>
</table>
| WBC          | - Very low sensitivity, low predictive value and low specificity, particularly in chronic PJI  
- Adds little to improve accuracy of diagnosis (2, 3) |
| ESR          | - Non-specific inflammatory marker  
- Also positive in anemia, cancer, connective tissue disorder  
- Returns to normal after surgery within 90 days up to one year (therefore it is not appropriate especially for diagnosing early postoperative infection)  
- High sensitivity below cut-off of 30 mm/h  
- Standard values differ between men and women (men: 3-15 mm/h, women 6-20 mm/h) |
| PCT          | - Non-specific inflammatory marker for surgical infections  
- Low sensitivity for local infection  
- Not a routine (still in research/validation)  
- Brings no additional information to CRP at significantly higher costs |
| CRP          | - Non-specific inflammatory marker  
- Unaffected by age, sex, anaesthesia, blood loss  
- Affected by steroids, immunosuppressives, postoperative haematoma  
- Returns to normal after surgery within 1-2 weeks  
- High sensitivity below cut-off of 10 mg/l  
- Levels can be within normal range in up to 30% of low grade infections  
- A serial determination of CRP gives more information and helps to evaluate possible PJI |
| IL-6         | - Specially for control of highly acute infections, not substantial for chronic infections  
- Return to normal (10 pg/ml) after surgery within three days  
- Not a routine (still in research/validation), high costs |
Value of blood tests for diagnosing PJI

Serum markers of inflammation play an important role for screening patients at risk in as far as results below the cut-offs (CRP, 10 mg/l; ESR 30 mm/h) help to exclude an infection (5–7). However, blood tests of inflammatory markers are neither sufficiently sensitive nor specific enough to diagnose or exclude PJI with high accuracy (1,5,8). Serial post-operative measurements should be preferred over single values for accurate interpretation of the results (1,9).
A combination of CRP and ESR is reported to have high predictive value (7) but cannot exclude infection 100%.

A combination of different diagnostic studies is usually required to diagnose PJI. These include blood tests, synovial fluid leukocyte count and differential as well as imaging studies.

**Acute infection**

CRP is elevated during an uneventful early postoperative period and normally drops within days. Therefore persistent elevation or any increase of CRP indicates infection.

In early acute infection, serum inflammatory markers may be missing (5,10).

**Chronic infection**

CRP determination has significance for detecting infection in patients with chronic symptoms, but without comorbidities that affect the test results (5).

In low-grade or chronic PJI inflammatory marker values may be within the normal range (5,10). Inflammatory markers do not allow exclusion of persistent infection prior to reimplantation in case of a 2-stage exchange (5,11).

---

**LEARNING POINTS**

*Remember that no inflammatory marker test is sufficiently sensitive or specific enough to definitively diagnose or exclude PJI alone.*

*A CRP value below the cut-off helps you to rule out infection in acute situations (5-7). Low grade infection values can be within the normal range.*

*Reevaluate a patient within 3 months who is at lower probability for PJI and without planned reoperation but who has abnormal CRP levels (6).*

*You will need further diagnostic tests especially in low-grade or chronic PJI. In this case, synovial fluid leukocyte count and differential is the most important test.*

*You should prefer serial post-operative measurements over single determinations (1, 9).*
References


2.5 Correct preoperative sampling. How to perform joint fluid aspiration to guarantee best results

Technical considerations – correct sampling

Aspiration of the knee joint can usually be performed in the office without imaging using a standard 18 or 20 G needle with or without a stylet. Smaller gauge needles may lead to difficulties in aspiration. In hip aspiration, spinal needles (20 G) are typically required. It is recommended to keep the stylet in place until the joint has been entered to prevent soft tissue from blocking the needle tip. Smaller needles should not be used because of the risk of bending and possible difficulties when withdrawing synovial fluid. In challenging situations, radiographic guidance and technical expertise of radiology may be necessary to obtain joint fluid.

In order to prevent both iatrogenic infection and false-positive results (S. epidermidis!), the aspiration of a prosthetic joint must be performed under strictly aseptic conditions (disinfection, sterile covering, use of sterile gloves and surgical mask). The risk of iatrogenic infection under aseptic conditions is extremely low (<0.01%). Aspiration through skin lesion (e.g. psoriasis) must be avoided. Toponarcsis only subdermal (toponarcsis in the joint leads to false-negative results because it can influence the cell count).

If possible aspiration should be performed sterile in the operation theatre under control of an image converter (especially hip aspiration). A "dry" joint can be washed with nonbacteriostatic saline to obtain material for culture, but this fluid then cannot not be used for synovial leukocyte count and differential.
Material needed for joint fluid aspiration: a) Local anaesthesia with a long infiltration needle (cutaneous and subcutaneous application only. Local anaesthetic in the joint may interfere with bacterial growth!) b) No. 11 blade for stab incision c) Long biopsy needle and 20 ml syringe, diameter 1.5–2.0. d) EDTA tube (white blood cell count and differentiation, crystals, protein, glucose, PCR) at least 1 ml, invert 5 x to prevent coagulation. e) Blood culture vials (aerobic and anaerobic). Following disinfection of the stopper, first insert at least 1 ml, preferably up to 5 ml, into the aerobic vial then without air into the anaerobic vial. f) Native tube for bacteriology (at least 1 ml) (9)

Handling of the aspiration fluid

Aspiration fluid should be sent for synovial fluid leukocyte count and differential (in a vial containing anticoagulants) as well as for Gram stain and culture (in a plain vial). Cell count and differential should have priority over culture. Positive cultures further confirm PJI and allow specification and resistance testing of the infecting organisms.
Leukocyte count must be performed within 24 hours of sampling.
Inoculation into blood bottle cultures improves sensitivity of culture. At least 1–2 ml samples should be taken.
Inoculate aerobic & anaerobic blood culture flasks with one part and transfer rest into EDTA tubes for cytology.
Add anticoagulants (EDTA, heparin) for determination of cell count and differential, and immediately softly shake it, to ensure that EDTA and aspiration fluid are mixed and no coagulation takes place. In case of high viscosity of the synovial-fluid add hyaluronidase. Pay attention to correct and careful labelling of the samples. In case microbiology department cannot process samples in time store aspiration fluid in sterile container at 4 °C.

**No systemic antibiotics before aspiration and culture!**

Systemic antibiotics should not be administered to a patient with suspected PJI before aspiration of joint fluid and, if surgery is indicated, before an intraoperative tissue culture has been obtained, unless required. Systemic antibiotics decrease the probability to identify the organism at the time of aspiration\(^8\). If antibiotics were administered before they should be stopped at least two weeks before sampling.
LEARNING POINTS

Synovial fluid leukocyte count and differential are the most important preoperative diagnostic tests for delayed (low-grade) PJI.

Allow antibiotic washout for at least 2 weeks before sampling.

Perform the aspiration under strictly aseptic conditions to prevent contamination.

Aspirate at least 1–2 ml synovial fluid from each of 3 different regions under strictly aseptic conditions.

Synovial fluid leukocyte count must be performed within 24 hours in a vial containing anticoagulants.

Ensure cooperation with a microbiologist specialized in orthopaedic infections (orthopaedic microbiology service).

Extend culture time to 10–15 days to detect slow growing microorganisms (e.g. Propionibacterium acnes). But remember: longer incubation can lead to more contamination.

In case of negative culture but high suspicion for infection, consider repeating aspiration.

References

2.6 Preoperative diagnostics. What are the most important preoperative methods for detecting PJI?

Any painful joint replacement has to be considered infected until proven otherwise. Signs and symptoms together with clinical history raise suspicion of PJI, and further diagnostics is mandatory to prove infection.

**Combination of tests required**

No single test, but a combination of different diagnostic studies is usually required to diagnose PJI\(^1,2\). As there are different types of PJI each situation requires different diagnostics. While acute infections are most of the time easy to diagnose because of clear **clinical signs** and high-virulent pathogens, especially for chronic infection **synovial fluid leukocyte count and differential** are the crucial preoperative tests.

**Synovial fluid leukocyte count and differential**

Traditionally, the presence or absence of PJI was determined by bacterial culture of aspiration fluid. Culture required several days before confirmation or exclusion of the diagnosis, frequently delaying patient care\(^39\). Especially sessile bacteria in the biofilm are a problem, some microorganisms need prolonged incubation up to 14 days, or yet there is no sufficient amount of microorganisms in the aspiration fluid for culturing.

In contrast, synovial fluid leukocyte count and differential are simple, rapid and accurate tests for differentiating prosthetic-joint associated infection from aseptic failure with high sensitivity and specificity that can be performed in most institutions before surgery\(^4,5\). Synovial leukocyte count and differential can be used alone or together with serologic tests such as CRP testing to accurately determine the probability of joint infection\(^3\).
Leukocyte count (A) and percentage of neutrophils (B) in the synovial fluid of patients with aseptic loosening and PJI (the broken lines indicate the cut-off values) (4)

<table>
<thead>
<tr>
<th></th>
<th>Native joints</th>
<th>Prosthetic joints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Septic Arthritis</td>
</tr>
<tr>
<td>Leukocytes, x 10⁹/L</td>
<td>&lt;0.2</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>&lt;25</td>
<td>&gt;90</td>
</tr>
</tbody>
</table>

Cell counts in synovial fluid of patients with native and prosthetic joints* (4, 5)

* Excluded: early postoperative phase (3 months) and inflammatory joint diseases

At a glance: preoperative diagnostic measures

Clinical signs and symptoms: Clinical suspicion for infection is the starting point of further diagnostic procedures. Sinus tract, visible purulence from wound discharge or an abscess are clear signs for an infection. In chronic infections there is often only pain without other clinical signs.
The key preoperative test in chronic infection-aspiration of synovial fluid:
Synovial fluid leukocyte count and differential are by far the most important as well as simple, rapid and accurate tests for differentiating PJI from aseptic failure with high sensitivity and specificity. These tests can easily be performed in most institutions before surgery\(^1\),\(^2\),\(^3\). Synovial fluid samples should be taken for culture, too, but cell count and differential have priority. Remember that the cell count is not significant up to six weeks postoperative and for patients with rheumatic diseases or leukopenia. The number of leukocytes is always high when there is an infection. So in suspected hematogenous infections leukocyte counts within the normal range can be used to exclude PJI. Leukocyte count is not relevant in early acute infections. Other biomarkers like alpha-defensin, leukocyte esterase or d-lactate in synovial fluid are currently tested with different results. These methods need to be validated and may in the future be integrated in the diagnostic process.

**Culturing** of the synovial fluid is used to detect the pathogens. In acute infections culturing has good sensitivity because of the highly virulent microorganisms. Synovial fluid cultures are better (sensitivity 79–91%, specificity 100%) than swab cultures (sensitivity 40–80%; specificity 99%) or tissue samples (sensitivity 57–79%, specificity 81%)\(^9\)

In delayed PJI cases prolonged incubation time (up to 15 days) might be necessary.

**Inflammation markers:** No inflammatory marker test is sufficiently sensitive or specific enough to definitively diagnose or exclude PJI - by themselves. C-reactive protein (CRP) determination should be preferred over erythrocyte sedimentation rate (ESR) and/or procalcitonin measurement. CRP has significance in detecting infection in patients with chronic symptoms without comorbidities\(^6\) and may help to exclude infection in screening\(^6\)-\(^8\). Serial measurements should be preferred.

**Blood cultures** should be taken before antibiotic therapy is started to avoid false negative results. They are used to exclude concomitant bacteraemia and if there are concerns of metastatic infection\(^10\).

**Imaging:** Plain radiography, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound and bone scintigraphy may support the diagnosis of PJI. However, the absence of radiological signs does not exclude the presence of infection\(^2\). A negative bone scintigraphy scan can exclude infection with high probability due to its excellent sensitivity.

If joint pain persists, repeated aspiration should be considered. If all preoperative tests are negative, but clinical suspicion of PJI persists, tissue sampling should be performed through arthroscopy or open biopsy.
<table>
<thead>
<tr>
<th>Test</th>
<th>Cut-offs / key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synovial fluid analysis</strong></td>
<td>Leukocytes &gt; 2000/µl</td>
</tr>
<tr>
<td></td>
<td>Neutrophils &gt; 70%</td>
</tr>
<tr>
<td><strong>Blood tests</strong></td>
<td>CRP &lt;10 mg/l; &lt;5mg/l (low grade infection)</td>
</tr>
<tr>
<td></td>
<td>ESR &lt;30 mm/h</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>Radiography translucent line &gt; 2 mm or severe focal osteolysis</td>
</tr>
<tr>
<td></td>
<td>CT/MRI additional soft tissue abnormalities</td>
</tr>
</tbody>
</table>

Cut-offs and key findings indicative of PJI

**LEARNING POINTS**

Consider any painful joint replacement to be infected until proven otherwise.

No single test, but a combination of different diagnostic studies is usually required to diagnose PJI.

Synovial fluid leukocyte count and differential are the crucial preoperative tests for diagnosing chronic PJI.

If clinical suspicion persists despite negative test results, surgery for tissue sampling, sonication of prosthesis and culture should be performed.

Stop antibiotics at least two weeks prior to aspiration (if not 20–30% false-negative results in culturing are to be expected).

**References**


2.7 Correct intraoperative sampling. How to obtain significant results with intraoperative culture and histology

Periprosthetic tissue cultures are the current gold standard for the diagnosis of prosthetic joint infection. Besides the prosthesis itself they provide the most accurate specimens for detecting microorganism(s)\(^1-3\).

**Sampling of intraoperative cultures**

Perioperative prophylaxis at revision surgery should not be started until tissue specimens have been collected for culture\(^5\). It is important to stop any antimicrobial therapy at least 2 weeks prior tissue sampling for culture\(^4\). Delay surgical prophylaxis if necessary. The sampling technique should be meticulous. \(\geq 3\) intraoperative tissue specimens from representative areas should be taken for culture\(^3\). The lower the grade of inflammation, the more samples should be collected\(^6\).

Larger numbers of samples are collected if a difficult low-grade infection is expected\(^8\)

Swabs of sinus tracts or wounds have a low sensitivity and should be avoided. Swabs are associated with high risk of contamination.\(^6\)
False-negative rates can be substantially decreased by prolonged culture incubation of 7 to 14 days (anaerobes) on enrichment media and ultrasonic lavage of the implants (see Challenge 8: sonication) (7). Sonication is especially useful in patients who received antimicrobial therapy within 14 days of surgery, because it increases the sensitivity of the culture (6, 7).

Videotutorial: Intraoperative sampling. Tissue biopsie for culture and histology. Length: 01:32 min

**Microbiological studies**

Gram stain has low sensitivity (20%) and is today no longer relevant. For culturing put samples in native tubes under sterile conditions (sensitivity 60–80%, specificity 97%) To prove infection > 2/3 of the samples must be positive. For high virulent germs one positive culture is sufficient.

**Histopathological studies**

In addition to culture samples, specimens for histopathological studies should be collected.
≥ 5 samples for histopathology should be taken from the joint capsule, the synovial lining as well as from around acetabular, femoral and tibial components.
Intra-operative frozen section histology helps to detect occult infection. The presence of ≥ 5 polymorphonuclear leukocytes per high power field (HPF) indicates infection.

LEARNING POINTS

**Stop any antimicrobial therapy ≥ 2 weeks before intraoperative tissue sampling.**

**Obtain ≥ 3 different tissue specimens for culture.**

**Ensure cooperation with a microbiologist specialized in orthopaedic infections (orthopaedic microbiology service).**

**Request prolonged culture incubation of 7 to 14 days.**

**Take additional ≥ 5 tissue samples for histopathological studies and polymorphonuclear cell count.**

**Consider sonication of removed prosthesis or mobile parts for improved diagnosis of biofilm infection (7).**

References

2.8 Sonication. How to improve intraoperative diagnostic yield for PJI

Sonication (ultrasound) allows to detach microorganisms from the surface of the implant and to detect up to 10,000 times more bacteria in the sonication fluid than by tissue culture. The culture of samples obtained by sonication of prostheses is more sensitive than conventional periprosthetic tissue culture (85–95% vs. 70–85%) for the microbiologic diagnosis of hip and knee infection (1). Sonication is especially useful in patients who received antimicrobial therapy within 14 days of surgery, because microorganism surviving in biofilms can be detected in the sonication fluid. The benefit of sonication for the diagnosis of PJI has been described for a number of joints (2–4).

**Method of sonication**

The removed implant is transported to the microbiological laboratory in a sterile, solid and air-tight container (the use of bags increases the contamination risk and is not recommended). To decrease the risk of contamination put the implant directly in the transport box only touching it with the instruments not with the gloves. If the prosthesis is fixed with antibiotic-loaded cement put implant and cement in separate boxes. Antibiotics might be eluded from the cement and lead to false-negative cultures.

Send it as quickly as possible to the microbiological laboratory for sonication and culturing. The sonication fluid should be processed within four hours. If this is not possible, add Ringer’s solution and store at room temperature.
In the microbiological laboratory after addition of Ringer's solution or normal saline (covering about 80% of the implant), the container is vortexed for 30 seconds (alternatively it's possible to shake manually) and sonicated (40 kHz) for 1 minute. Finally, there is a last vortex step of 30 seconds (again manually shaking is possible) before plating out the sonication fluid. Vortexing alone without sonication yields worse results.\textsuperscript{(5,3)}
For sonication, low frequency and low intensity ultrasound at the threshold of microbubble formation (cavitation) is applied. Due to micro-currents of sonication fluid, shear forces and oscillating cavitation bubbles, biofilm is removed and the bacteria are disaggregated without significant cell destruction. The sonication fluid is cultured on aerobic and anaerobic agar plates and can be inoculated in broth media. If there are no results it can be used for alternative methods (e.g. PCR).

Videotutorial: Implant Sonication. Procedure and further microbiological testing. Length: 02:17 min

**Interpretation of results**

Since bacteria survive, but do not replicate in the sonication fluid, the method allows for quantitative assessment of removed biofilm. The microbial density is expressed as number of colony-forming units (CFU) per ml of sonication fluid. A cut-off of 50 CFU/ml sonication fluid yields a sensitivity of 85–95% and specificity of 95% for the diagnosis of PJI based on a study involving 331 patients with total knee or hip prostheses (1). Quantification of the number of microorganisms in the sonication fluid helps to distinguish infected from contaminated prostheses. In addition, the use of solid containers vs. bags for sonication reduces the risk of contamination (6).
Advantages of sonication over tissue biopsy

- Better sensitivity
- Quantitative (more specific)
- Detection of mixed infections
- Faster, less expensive
- Fluid for additional investigations

Sonication improves the detection of bacteria up to 10,000 times compared with periprosthetic tissue cultures

Alternative methods to detach biofilm

If sonication is not available other ways for detaching biofilm from the implant should be considered. Vortexing can be used alone but gives worse results. Manually detaching biofilm with a cytobrush has been reported with different results (due to subjective variations impacting the outcome of the procedure, the cytobrush technique should not be favoured)\(^7\). Bead beating is an alternative method shaking the implants in a solution containing small glass beads. Solvents decrease the viability of bacteria and hence sensitivity. Studies using dithiothreitol (DTT) to remove microorganisms from the biofilm on the prosthesis show similar results as sonication and might be a reasonable alternative to improve diagnostics\(^{15}\). This procedures still needs to be validated.
Additional investigations

The use of broad range polymerase chain reaction (PCR)\(^{(8)}\) and multiplex PCR\(^{(10,11)}\) from the sonication fluid improves diagnosis of implant infection, particularly in patients pretreated with antibiotics before sampling. Recently, a study performed multiplex PCR in 86 patients considerably improved sensitivity compared with culture (97% vs. 71%) with a specificity of 100%\(^{(11)}\). Since multiplex PCR kits do not contain specific primers for low-virulent organisms such as *Propionibacterium acnes* they have to be modified or combined with methods involving direct sequencing\(^{(12)}\).

Other newer diagnostic methods include microcalorimetry and mass spectrometry of sonication fluid\(^{(5,13)}\). These methods are able to identify the organism, but cannot determine antibiotic resistance. They still have to be tested for reliability and may in the future replace culture methods.

**LEARNING POINTS**

*Sonication of the implant and microbiological analysis of the sonication fluid is the easiest and most efficient method for intraoperative diagnosis of PJI and identification of the causative microorganism.*

*The sensitivity is particularly improved in patients having previously received antibiotics, due to better survival of bacteria in biofilm.*

*Place the implant compounds in sterile, solid and air-tide container and transport them immediately to the microbiological laboratory.*

**References**


2.9 Intraoperative diagnostics. What are the most important intraoperative methods to identify the microorganism?

If preoperative testing does not prove or exclude PJI, diagnosis has to be confirmed by surgery. The experience of the surgeon in diagnosing infection is important, but further microbiological, histological and possibly molecular testing is essential, in particular to be able to identify the infecting organism and its antimicrobial resistance.

**Intraoperative cultures and sonication**

The **gold standard** for intraoperative diagnosis of prosthetic joint infection is culture of tissue samples. Sampling should be meticulous and **at least 3 samples** from different sites should be taken.\(^{(1, 2)}\) Especially in low grade infections even intraoperative tissue samples may still be negative. Sensitivity of microbiological analysis can further be improved by **sonication** of the implant.\(^{\,(3)}\) This method allows quantitative assessment of bacteria in the removed biofilm. Sonication is especially useful in patients who received antimicrobial therapy within 14 days of surgery, because it increases the sensitivity of the culture.\(^{(2, 3)}\)

Microbiological analysis of tissue samples or sonication fluid is important to establish the appropriate therapeutic or prophylactic antibiotic regimen and to determine resistance to antibiotics.

**Histopathological studies**

Tissue should be sampled (at **least 5 samples**) for histopathology since results from histopathological studies can give further evidence of infection. The presence of polymorphonuclear leukocytes in intraoperative frozen section histology can indicate occult infection. For histopathological analysis neutrophil granulocytes are most important. You need to find in 10 fields of view (magnification factor 400) to be at least 5–10 granulocytes each to identify a low grade infection.
High-grade infection: (top, left) Synovial membrane with numerous granulocytes, high-grade infection, foreign body giant cells; (top, right) Large numbers of granulocytes with simultaneous presence of giant cells with phagocytised material.

Low-grade infection: (below, left) Isolated granulocytes; (below, right) Granulocytes much more visible with immunohistochemical staining (CD 15) (7)

**Molecular diagnosis**

Molecular diagnostics have recently been introduced to the diagnosis of PJI. Broad range or multiplex polymerase chain reaction (PCR) is a very sensitive and fast method to detect bacterial DNA, e.g., in sonication fluid (4–6). However, molecular biology tests are not yet available in every institution.
LEARNING POINTS

Culture of tissue samples is the gold standard for intraoperative diagnostics.

Consider sonication of the implant to improve sensitivity of the microbiological analysis.

Collect at least 5 samples for histopathological studies and consider intraoperative frozen section histology. Ensure cooperation with a microbiologist specialized in orthopaedic infections (orthopaedic microbiology service).

Take care that culture time is prolonged to 7 to 14 days in order to decrease false-negative rates\(^{(3)}\).

References

3. MEDIA LIBRARY

In the Media Library you find a list of current research literature topically sorted to give you a broad scientific background. For many basic information like definition and classification of PJI you find the most important figures and tables directly in the list. This allows surgeons of all levels of experience to gain basic knowledge prior to starting the learning cases and to gain insight in theoretical background later on. Checklists for PJI in general and all infection types summarize the diagnostic steps and can be used to implement your new knowledge into your everyday life.
### 3.1 Literature

**Bacterial culture incubation**


![Graph showing time required to grow different bacteria species](image)

<table>
<thead>
<tr>
<th>Time required to grow different bacteria species</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
</tr>
<tr>
<td>Coag.-neg. staphylococci</td>
</tr>
<tr>
<td>Enterococcus species</td>
</tr>
<tr>
<td>Streptococcus species</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Coryneform bacteria</td>
</tr>
<tr>
<td>Propionibacterium species</td>
</tr>
<tr>
<td>Peptostreptococcus species</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>

**Biofilm**


Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms.

Blood tests


Classification


<table>
<thead>
<tr>
<th>Pathogenesis:</th>
<th>Acute PJI</th>
<th>Chronic PJI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative</td>
<td>Early postoperative after surgery</td>
<td>Delayed (Low-grade) after surgery</td>
</tr>
<tr>
<td>Hematogenous or per continuitatem</td>
<td>&lt; 3 weeks of symptoms</td>
<td>≥ 3 weeks of symptoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biofilm age (maturity)</th>
<th>Acute PJI</th>
<th>Chronic PJI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immature (eradication possible)</td>
<td>Mature (eradication only possible with exchange of prosthesis)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Acute PJI</th>
<th>Chronic PJI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pain, fever, red/swollen joint</td>
<td>Chronic pain, loosening of the prosthesis, sinus tract (fistula)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Causative microorganism</th>
<th>Acute PJI</th>
<th>Chronic PJI</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-virulent: Staphylococcus aureus, gramnegative bacteria (e.g. E. coli, Klebsiella, Pseudomonas aeruginosa)</td>
<td>Low-virulent: Coagulase-negative staphylococci (Staphylococcus epidermidis), Propionibacterium acne</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical treatment</th>
<th>Acute PJI</th>
<th>Chronic PJI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Débridement &amp; retention of prosthesis (always with change of mobile parts)</td>
<td>Complete removal of prosthesis (exchange in one-, two- or multiple stages)</td>
<td></td>
</tr>
</tbody>
</table>

Classification for acute and chronic PJI
<table>
<thead>
<tr>
<th>Time after implantation</th>
<th>0-3 months</th>
<th>3-24 (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>Perioperative</td>
<td>Haematogenous</td>
</tr>
<tr>
<td>Signs</td>
<td>Acute: Fever, elusion, warmth, dehiscence</td>
<td>Chronic: Persistent pain, early loosening, sinus tract</td>
<td>Acute or subacute</td>
</tr>
<tr>
<td>Pathogen</td>
<td>S. aureus, Streptococci, Enterococci</td>
<td>Coagulase-negative staphylococci, P. acnes</td>
<td>S. aureus, E. coli</td>
</tr>
</tbody>
</table>

Classification according to the onset of signs and symptoms after implantation and to the route of infection

**COMMENT**

*Classification of PJI according to the status of biofilm (relevant for surgical treatment):*

*Acute infection with premature biofilm* → 1–4 weeks postoperative or in haematogenous cases less than three weeks of symptoms

*Chronic infection with mature biofilm* → More than 4 weeks of symptoms
Definition of PJI


A definite periprosthetic joint infection exists when:

- There is a sinus tract communication with the prosthesis
- A pathogen is isolated by culture from 2 or more separate tissue or fluid samples obtained from the affected prosthetic joint
- When 4 of the following 6 criteria exist:
  - Elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein concentration (CRP)
  - Elevated synovial white blood cell count
  - Elevated synovial neutrophil percentage (PMN%)
  - Presence of purulence in the affected joint
  - Isolation of a microorganism in 1 culture of periprosthetic tissue or fluid
  - Greater than 5 neutrophils per high power field in 5 high power fields observed from histological analysis of periprosthetic tissue at 400x magnification

Recent algorithm of Musculoskeletal Infection Society

COMMENT

Some authors challenge these above suggested criteria since the presence of each criterion alone, such as purulence, positive histopathology and increased white blood cell count in synovial fluid, are sufficient for diagnosis of PJI.
Definition criteria for PJI commonly used

### Clinical features

- Sinus tract (fistula) communicating with the prosthesis or visible purulence (wound secretion, pus) around the prosthesis
- Sensitivity: 20-30%
- Specificity: ~100%

### Histology

- Acute inflammation in periprosthetic tissue
- Sensitivity: 95-98%
- Specificity: 98-99%

### Cell count in joint aspirate

- > 2000 µl leukocytes or > 70% granulocytes (PMN)
- Sensitivity: 93-96%
- Specificity: 97-98%

### Microbiology

- Microbial growth in:
  - Synovial fluid or
  - > 2 tissue samples or
  - Sonication fluid (≥ 50 CFU/ml)
- Sensitivity: 60-80%
- Specificity: 97%
- Sensitivity: 70-85%
- Specificity: 92%
- Sensitivity: 85-95%
- Specificity: 95%

---

*a Metal-on-metal bearing components can simulate pus («pseudopus»), but leukocyte count is normal (visible metal debris)

*b Acute inflammation defined as > 2 granulocytes per high-power field (= type 2 or 3 after Krenn and Morawietz)

*c Leukocyte cutoffs are not interpretable within 6 weeks of surgery, in rheumatic joint disease, periprosthetic fracture or luxation. Leukocyte count should be determined < 24 h by microscopy or automated counter; clotted specimens are treated with 10µl hyaluronidase

*d For highly virulent microorganisms (e.g., *S. aureus*, *E. coli*) already one positive sample confirms infection

*e Under antibiotics and for anaerobes, < 50 CCFU/ml can be significant

---

**Diagnostic algorithms**

COMMENT

Some authors do not recommend using blood tests (ESR and CRP) for diagnostic workup for PJI as up to 30% of low grade infections have normal values of biomarkers in blood. In case of painful joint prosthesis aspiration for culture and white blood cell count is recommended independent of the value of ESR and CRP.

Acute symptoms

- Clinical examination
- Laboratory tests (CRP)
- X-ray (prosthetic joint)

Previous surgery < 4 weeks ago (early postoperative)

Punctio sicca?        Joint aspiration

c no

Exclusion of non-infectious pathology
periprosthetic fracture, dislocation, muscular pathology, etc.

Persistent suspicion of infection

Microbiology:
consistent with infection?

Leukocytes:
>200/μl or >10% granulocytes?

no

no

yes

yes

Perioperative route

Perprosthetic joint infection

Septic revision and intraoperative diagnostics

Per continuitatem

Hematogenous

Investigation of cause

Blood cultures

negative

positive

Search for infectious focus:
- Examination of skin (cellulitis?)
- Imaging of abdomen/pelvis (abscess?) and spine (vertebral osteomyelitis?)

Search for primary focus:
- TEE (vegetation?)
- Orthopantomogram
- Intravascular device (catheter, port, ICD/pacemaker?)
- Urinalysis
- X-ray of lung

Pathogenesis

1 Leukocyte cutoffs are not interpretable within 6 weeks of surgery in rheumatic disease, periprosthetic fracture, dislocation.
2 For highly virulent organisms (e.g., S. aureus, E. coli) already one positive sample confirms infection, for low-virulent organisms (e.g., S. epidermidis, P. acnes) >2 positive samples are required to confirm infection.
3 Elevated CRP, fever, local erythema
4 According to treatment algorithm for PJ
5 Leukocyte count, microbiology (including sonication), histopathology
Algorithm for acute and chronic PJI

Algorithm for acute and chronic PJI
Diagnostic methods


Preoperative and intraoperative diagnostic methods


<table>
<thead>
<tr>
<th>Preoperative methods</th>
<th>Intraoperative methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td><strong>Tissue specimens</strong></td>
</tr>
<tr>
<td>L, ESR, CRP, PCT</td>
<td>Histopathology</td>
</tr>
<tr>
<td></td>
<td>Gram / Culture</td>
</tr>
</tbody>
</table>

| Imaging              | New methods            |
| X-ray                | Sonication             |
| MRI, PET, CT         | PCR                    |
| Scintigraphy         | Microcalorimetry       |
|                      | Mass spectrometry      |

<table>
<thead>
<tr>
<th>Synovial fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count</td>
</tr>
<tr>
<td>Gram / Culture</td>
</tr>
<tr>
<td>EC-Esterase</td>
</tr>
</tbody>
</table>

Conventional, new and innovative diagnostic methods

<table>
<thead>
<tr>
<th>Conventional diagnostic methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>laboratory markers</td>
</tr>
<tr>
<td>histopathology</td>
</tr>
<tr>
<td>synovial fluid</td>
</tr>
<tr>
<td>periprosthetic tissue cultures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New diagnostic methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>sonication of implants</td>
</tr>
<tr>
<td>specific and multiplex PCR</td>
</tr>
<tr>
<td>mass spectrometry</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Innovative techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>new laboratory markers</td>
</tr>
<tr>
<td>microcalorimetry</td>
</tr>
<tr>
<td>electrical method</td>
</tr>
<tr>
<td>reverse transcription (RT)-PCR</td>
</tr>
<tr>
<td>fluorescence in situ hybridization [FISH]</td>
</tr>
<tr>
<td>biofilm microscopy</td>
</tr>
<tr>
<td>microarray identification</td>
</tr>
<tr>
<td>serological tests</td>
</tr>
</tbody>
</table>

Epidemiology

Data on frequency of PJI (according to different registers)

<table>
<thead>
<tr>
<th></th>
<th>two years after primary joint replacement</th>
<th>two years after revision surgery</th>
<th>Entire lifetime of prosthetic joint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip, shoulder</td>
<td>&lt; 1%</td>
<td>up to 40%</td>
<td>Haematogenous seeding reported as incidence rate (per prosthesis-year) 0,2%</td>
</tr>
<tr>
<td>Knee</td>
<td>&lt; 2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbow</td>
<td>&lt; 9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Reasons for revision after known primary total hip replacement by the AOA NJRR for 2009

History / clinical diagnosis


Aseptic biomechanical failure

### Mechanism

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Wear debris</td>
<td>Loss of material with generation of particles resulting from relative motion between opposed surfaces (Adhesive or fatigue wear). Inflammatory reaction to particles of orthopaedic wear debris causes bone resorption</td>
</tr>
<tr>
<td>B. Eccentric mechanical loads</td>
<td>Misaligned arthroplasty alters the magnitude and direction of load transmission through the prosthesis and causes implant loosening and mechanical damage to the implant material or the interface between implant and bone</td>
</tr>
<tr>
<td>C. Implant motion</td>
<td>Micromotion of loose prosthesis leads to progressive bone resorption.</td>
</tr>
<tr>
<td>D. Hydrodynamic pressure</td>
<td>Synovial fluid is compressed through defects of the prosthesis and host bone. This effect is likely amplified in the presence of excessive wear debris.</td>
</tr>
</tbody>
</table>

### Imaging


<table>
<thead>
<tr>
<th>Type of imaging</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-Ray</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>CT</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>MRI</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Nuclear medicine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{99m}$Tc bone scan</td>
<td>100</td>
<td>5-23</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>$^{67}$Ga Gallium scan</td>
<td>50</td>
<td>78</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>$^{111}$In leukocytescan</td>
<td>38-83</td>
<td>88-100</td>
<td>58</td>
<td>94</td>
</tr>
<tr>
<td>Combined bone/WBCs</td>
<td>66</td>
<td>98</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>$^{99m}$Tc HMPAO leukocyte scan</td>
<td>100</td>
<td>82</td>
<td>67</td>
<td>100</td>
</tr>
<tr>
<td>$^{99m}$Tc antigranulocyte antibody scan</td>
<td>100</td>
<td>58</td>
<td>57</td>
<td>100</td>
</tr>
<tr>
<td>$^{111}$In-IgG scan</td>
<td>92</td>
<td>88</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>$^{99m}$Tc-ciprofl oxacin, knee</td>
<td>86</td>
<td>78-92</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Infection, hip</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>$^{18}$FDG-PET scan, knee</td>
<td>91</td>
<td>72</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>$^{18}$FDG-PET scan, hip</td>
<td>90</td>
<td>89</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

FDG - fluorodeoxyglucose; HMPAO – hexamethyl propyleneamine oxime; In – indinium; ND – no data available; NPV – negative predictive value; PET – positron emission tomography; PPV – positive predictive value; Tc – technetium
Radiological and nuclear medicine imaging of infected prosthetic joints


Intraoperative diagnostics


![Graph showing sensitivity of culture and multiplex PCR of sonication fluid](image)

Sensitivity of culture and multiplex PCR of sonication fluid (NS – not significant; eight pathogens were missed by PCR due to lack of specific primers for these species: 7 Propionibacterium acnes and 1 Corynebacterium species)


Sensitivity and specificity for commonly used intraoperative definition criteria for PJI


Effect of preoperative antimicrobial therapy on culture sensitivity in patients with prosthetic joint infection (Periprosthetic tissue culture was defined as positive if the same organism was grown from two or more specimens. Sonicatie-fluid culture was defined as positive if more than 5 colony-forming units of the same organism grew on the aerobic or the anaerobic plate.)
Intraoperative sampling


Joint fluid aspiration


Pathogenesis

Incidence of exogenous vs. endogenous PJI after primary implantation


<table>
<thead>
<tr>
<th>Difficult-to-treat</th>
<th>Difficult-to-detect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin-resistant staphylococci</td>
<td>Anaerobes (Propionibacterium acnes, Peptostreptococcus, Finergoldia)</td>
</tr>
<tr>
<td>Enterococci (all)</td>
<td>Small colony variants</td>
</tr>
<tr>
<td>Quinolone-resistant Gram-negative bacilli</td>
<td>Nutrionally variant streptococci (NVS): Abiotrophia and Granulicatella species</td>
</tr>
<tr>
<td>Fungi (Candida)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence of exogenous infection</th>
<th>Evidence of haematogenous infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative staphylococci (CNS)</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>Viridans group streptococci</td>
</tr>
<tr>
<td>Corynebacterium species</td>
<td>Gram-negative Bacilli</td>
</tr>
</tbody>
</table>

Difficult-to-treat vs. difficult-to-detect microorganisms

**COMMENT**

*MRSA belongs not to difficult-to-treat microorganisms as long as it is susceptible to rifampicin.*
Preoperative diagnostics


<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Journal</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Alijanipour et al. (1)</td>
<td>CORR</td>
<td>Knee 10mg/l</td>
<td>97%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hip 10 mg/l</td>
<td>88%</td>
<td>77%</td>
</tr>
<tr>
<td>2012</td>
<td>Costa et al. (2)</td>
<td>Am J Ortho</td>
<td>10 mg/l</td>
<td>93%</td>
<td>40/</td>
</tr>
<tr>
<td>2010</td>
<td>Piper et al. (3)</td>
<td>Plos One</td>
<td>Knee 14.5 mg/l</td>
<td>79%</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hip 10.3 mg/l</td>
<td>74%</td>
<td>79%</td>
</tr>
<tr>
<td>2009</td>
<td>Ghanem et al. (4)</td>
<td>Int J Inf Diseases</td>
<td>20.5 mg/l</td>
<td>94%</td>
<td>81%</td>
</tr>
<tr>
<td>2007</td>
<td>Nilsdotter-Augustinsson et al. (5)</td>
<td>Acta Ortho</td>
<td>10mg/l</td>
<td>82%</td>
<td>71%</td>
</tr>
<tr>
<td>2007</td>
<td>Greidanus et al. (6)</td>
<td>JBJS</td>
<td>13.5 mg/l</td>
<td>91%</td>
<td>86%</td>
</tr>
<tr>
<td>1999</td>
<td>Spanghel et al. (7)</td>
<td>JBJS</td>
<td>10 mg/l</td>
<td>96%</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Average</td>
<td>87%</td>
<td>77%</td>
</tr>
</tbody>
</table>

Serum CRP

COMMENT

Problem: Non-specific for joint infection.


**Sedimentation Rate – ESR**

**COMMENT**

*Positive result is not specific for joint infection. Multiple conditions can lead to elevated ESR*


**PCR (* Assessed three different types of PCR)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Journal</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Bonilla et al.</td>
<td>Diagnostic Micro and InfecDis</td>
<td>63%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>63%</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>44%</td>
<td>100%</td>
</tr>
<tr>
<td>2008</td>
<td>Gallo et al.</td>
<td>New Microbiol</td>
<td>71%</td>
<td>97%</td>
</tr>
<tr>
<td>2007</td>
<td>Fihman et al.</td>
<td>Journal of Infection</td>
<td>54%</td>
<td>86%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Average</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>59%</td>
<td>96%</td>
</tr>
</tbody>
</table>
COMMENT

*Poor sensitivity, by increasing sensitivity unexpectedly high rate of bacterial detection.*


Ghanem E, et al. The use of receiver operating characteristics analysis in determining erythrocyte sedimentation rate and C-reactive protein levels in diagnosing periprosthetic infection prior to revision total hip arthroplasty. Int J Inf Diseases (2009) 13, e444–e449. (4)


<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Journal</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>Gomez et al. (8)</td>
<td>J ClinMicro</td>
<td>64%</td>
<td>97%</td>
</tr>
<tr>
<td>2008</td>
<td>Gallo et al. (9)</td>
<td>New Microbiol</td>
<td>44%</td>
<td>94%</td>
</tr>
<tr>
<td>2006</td>
<td>Bare et al. (10)</td>
<td>CORR</td>
<td>53%</td>
<td>94%</td>
</tr>
<tr>
<td>1999</td>
<td>Spangehl et al (7).</td>
<td>JBJS</td>
<td>71%*</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td></td>
<td>59%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Synovial Fluid Culture (* when including patients on preoperative antibiotics)

COMMENT

*Low sensitivity due to culture technique and low bacterial counts. Can be affected by antibiotics.*


### Synovial Fluid WBC count

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Journal</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Dinneen et al. (11)</td>
<td>JBJS (BR)</td>
<td>1590 cells/mm³</td>
<td>90%</td>
<td>91%</td>
</tr>
<tr>
<td>2012</td>
<td>Zimistowski et al. (12)</td>
<td>JOA</td>
<td>3000 cells/mm³</td>
<td>93%</td>
<td>94%</td>
</tr>
<tr>
<td>2010</td>
<td>Shukla et al. (13)</td>
<td>JOA</td>
<td>3528 cells/mm³</td>
<td>78%</td>
<td>96%</td>
</tr>
<tr>
<td>2008</td>
<td>Ghanem et al. (14)</td>
<td>JBJS</td>
<td>1100 cells/mm³</td>
<td>91%</td>
<td>88%</td>
</tr>
<tr>
<td>2007</td>
<td>Nilsdotter-Augustinsson et al. (5)</td>
<td>Acta Ortho</td>
<td>1700 cells/mm³</td>
<td>86%</td>
<td>92%</td>
</tr>
<tr>
<td>2004</td>
<td>Trampuz et al. (15)</td>
<td>Am J med</td>
<td>1700 cells/mm³</td>
<td>94%</td>
<td>88%</td>
</tr>
</tbody>
</table>

**Average**

|         |         |         |         | 89%       | 92%       |

### Leukocyte Esterase Test Strip

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Journal</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>W weters el. (16)</td>
<td>JOA</td>
<td>93%</td>
<td>89%</td>
</tr>
<tr>
<td>2011</td>
<td>Parvizi el. (17)</td>
<td>JBJA</td>
<td>81%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Average**

|         |         |         |         | 87%       | 95%       |

### COMMENT

*May be affected by inflammatory conditions or immunocompromise.*

---


COMMENT

Up to 30% of samples cannot be interpreted due to blood and debris.


Risk factors


<table>
<thead>
<tr>
<th>Arthroplasty procedure</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Poor nutritional status</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Concurrent UTI (urinary tract infection)</td>
</tr>
<tr>
<td></td>
<td>Steroid therapy</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
</tr>
<tr>
<td></td>
<td>Postoperative surgical site infection</td>
</tr>
<tr>
<td></td>
<td>NNIS (National Nosocomial Infection Surveillance score) &gt; 0</td>
</tr>
<tr>
<td>Revision (if done for infection)</td>
<td>Prior joint surgery</td>
</tr>
<tr>
<td></td>
<td>Prolonged operating room time</td>
</tr>
<tr>
<td></td>
<td>Preoperative infection (of teeth or skin, or UTI)</td>
</tr>
</tbody>
</table>

Risk factors for PJI in primary versus revision arthroplasty of the hip or knee

Continuous and categorical variables used to identify possible predictors of PJI

### Preoperative variables

**Demographic factors:** Gender, age, ethnicity, height, weight, body mass index

**Patient medical factors:**
- American Society of Anesthesiologists score, alcohol abuse, hypertension, hyperlipidemia, diabetes mellitus, rheumatoid arthritis, cardiac arrhythmias, coronary heart disease, peripheral vascular disease, congestive heart failure, cardiac transplant, cardiac valvular disease, dementia, stroke, neurologic disease (paralysis, dyskinesia, Parkinson), renal insufficiency, renal failure and dialysis, anemia (aplastic, autoimmune, iron deficiency), coagulopathy, urinary tract infection, liver disease (hepatitis B, hepatitis C, hepatic insufficiency), malignancy (all visceral, metastatic and melanoma), tuberculosis, venous thromboembolic disease

**Preoperative laboratory values:** Hemoglobin, international normalized ratio (INR), leukocyte count, glucose, creatinine, albumin

### Surgical and postoperative variables

**Surgery:** Joint operated (hip versus knee), side (unilateral, simultaneous bilateral), operative time (minutes)

**Blood management:** Transfusion (yes or no, number of units transfused, type of transfusion—allogenic versus autologous)

**Postoperative laboratory values:** Hemoglobin, INR, leukocyte count, glucose, creatinine, albumin

**Postoperative medical complications:** Urinary tract infection, pneumonia, Clostridium difficile-associated diarrhea, pulmonary embolism, acute myocardial infarction, arrhythmia, congestive heart failure, atrial fibrillation, stroke, deep venous thrombosis, lung aspiration, fever

**Postoperative local complications:** Cellulitis, hematoma, wound infection, wound drainage, wound dehiscence, blisters, vascular injury, compartment syndrome, dislocation

### Sonication


Spectrum of microorganisms


<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Frequency (%)</th>
<th>Virulence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>30-43</td>
<td>Low</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>12-23</td>
<td>High</td>
</tr>
<tr>
<td>Streptococci</td>
<td>9-10</td>
<td>Medium</td>
</tr>
<tr>
<td>Enterococci</td>
<td>3-7</td>
<td>Medium</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>3-7</td>
<td>High</td>
</tr>
<tr>
<td>Anaerobes (e.g. <em>Bacteroides spp.</em>, <em>Propionibacterium acnes</em>)</td>
<td>2-4</td>
<td>Low</td>
</tr>
<tr>
<td><em>Candida</em> spp.</td>
<td>1-3</td>
<td>Low</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>10-20</td>
<td>Variable</td>
</tr>
<tr>
<td>Unknown (culture false-negative)</td>
<td>10-25</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Frequency of microorganisms causing PJI

COMMENT

Probably several aseptic loosenings are unrecognized low grade septic failures. With improved diagnostic methods these microorganisms will be more often detected and may change the frequency.

Therapeutic options

Algorithm for treatment of PJI

(* 1. Rifampicin-resistant staphylococci / 2. Enterococci (all) / 3. Quinolone-resistant Gram-negative bacilli / 4. Fungi (Candida). According to new data MRSA/MRSE not DTT as long as it is not rifampicin resistant)

COMMENT

A current unpublished study with 40 patients at the Charité University Medicine in Berlin following the above mentioned treatment algorithm shows in retrospect the short interval to be superior to the long interval both regarding infection management and function. The failure rate lies at 10% for short interval compared to 30% for the long interval. The overall good success rates of the algorithm cannot only be ascribed to the surgical approach but also to an optimized antibiotic treatment, which allowed to reduce the failure rate for the long interval. The close teamwork between surgeon and infectiologist/microbiologist is again proven to be essential for successful management of PJI.
Surgical and antibiotic treatment concept
3.2 Working tools

Checklist “low grade (delayed) infection”

The diagnostic process in low grade infections

Step 1: History

- The diagnostic routine starts with detailed history: risk factors and the interval to primary surgery give first hints on the type of the possible infection. Two to three years after surgery are the crucial time period for developing low grade PJI.

Step 2: Clinical symptoms and physical examination

- In case of low grade infection there are often no clinical symptoms. In presence of a pain within the first years after implantation of a joint prosthesis low grade PJI should be considered until proven otherwise.

Step 3: Imaging

- Early implant loosening is a clear hint for low grade infection. Some infections progress very slowly so the implant loosening is not yet visible at an early stage.
- Imaging techniques can’t detect an infection but help you to find other reasons for pain. In many cases differentiation between septic and aseptic loosening is difficult. Nevertheless infection must be ruled out in case of implant loosening etc.
- Conventional radiographs are sufficient as first imaging procedure. In complex situations other imaging techniques should be discussed.

Step 4: Laboratory Diagnostics

- No inflammatory marker has adequate sensitivity and specificity to approve or to exclude PJI. It is important not only to look at the values of blood tests but at the dynamics of the value. While in acute infection they are elevated and constantly rising in chronical infection levels can be within
the normal range.

Step 5: Preoperative microbiology and histopathology

• In preoperative diagnostic many microorganisms often can’t be identified. But: Positive microbiology is not compulsory for diagnosing PJI.
• The number of required samples is based on the class of infection. If low grade infection is suspected, five or more samples are needed
• Important for histophathology and microbiology is the avoidance respectively the stop of antibiotic treatment at least minimum two weeks prior to the testing and correct sampling.
• Always determine synovial-fluid leukocyte count. Remember that the cell count is not significant up to six weeks postoperative and for patients with rheumatic diseases or leukopenia.

Step 6: Intraoperative microbiology and histopathology

• In case of loosening the implant can’t be retained. The removal of the prosthesis allows the detachment of adherent bacteria directly from the implant or the bone cement.
• Slow growing bacteria (e.g. Propionibacterium acnes) need prolonged microbiological culturing for 2 weeks (bacterial culture incubation) or even special diagnostic methods like PCR or mass spectrometry.
• An increase of diagnostic validity is given by the combined interpretation of sonication findings and histopathological consensus-classification.

Step 7: New methods

• The best diagnostic tool is the prosthesis itself. The detachment of adherent bacteria is intraoperative possible via sonication of the implant.

Step 8: Treatment and postoperative follow-up

Successfull management of infection needs a team. PJI always requires a combination of surgery and antibiotic therapy. Treatment must be adapted to the individual clinical situation.

LEARNING POINTS

No single laboratory test has perfect sensitivity and specificity for diagnosing infection. A combination of laboratory, histopathology, microbiology & imaging studies gives best results. Remember: If there is only one indication PJI must be suspected and excluded.
Checklist “acute haematogenous infection”

The diagnostic process in acute haematogenous infections

**Step 1: History**

- The diagnostic routine starts with detailed history: The interval to primary surgery gives a first hint on the type of the possible infection. Main risk factor for haematogenuous infection of orthopedic prosthesis is bacteraemia. They are caused endogeneously mostly by skin inflammation, lunge inflammation, urinary tract infection, intestinal infection or tooth infection. The risk of haematogenous infection exists throughout life and is cumulating over the years.

**Step 2: Clinical symptoms and physical examination**

- In haematogenous infections local signs of prosthetic joint infection may present after several days. Therefore daily targeted examination of all joints, especially prosthetic joints is important.

**Step 3: Imaging**

- If a patient has more than one joint prosthesis it is important to check all of them accurately using scintigraphy, PET or joint aspiration.

**Step 4: Laboratory Diagnostics**

- A high CRP level (between 50 and 400 mg/l) is typical in case of haematogenous infection. Due to the bacteraemia not only CRP levels but all biomarker are elevated.
- Should CRP/biomarker levels do not steadily decrease after treatment other infectious foci should be excluded (septic thrombosis, endocarditis, other bone or joint infection, e.g. vertebral osteomyelitis).

**Step 5: Preoperative microbiology and histopathology**

- If PJI is not clear a puncture should always be performed to diagnose the infection and isolate the causing microorganism.
- It is important to start the treatment fast so the infection cannot spread to other joints, regions or organs. But remember to take at least blood cultures before starting the antibiotic therapy.
• In rare cases cultures are negative, especially of samples after start of antibiotic treatment: then gram stain from sonication fluid (50% sensitivity) and PCR can detect the microorganisms.

Step 6: Intraoperative microbiology and histopathology

• The goal for the diagnosis and treatment of haematogenaus infections should be the retention of the prosthesis if possible. If one debridement is insufficient (approx. 20%) a second debridement is needed again accompanied by the change of all mobile parts.
• Intraoperative diagnostic methods (tissue biopsy and implant sonication) should be used to verify the diagnosis and facilitate a targeted antibiotic therapy.

Step 7: Treatment and postoperative follow-up

Successful management of infection needs a team. PJI always requires a combination of surgery and antibiotic therapy. Treatment must be adapted to the individual clinical situation.

LEARNING POINTS

In case of haematogenous infections it is important to act fast (as retention of the prosthesis is only possible within the first 3 weeks after the start of symptoms) and to avoid the spread of the infection.

Checklist “early postoperative infection”

The diagnostic process in early postoperative infections

Step 1: History

• If a prosthesis gets infected up to 4 weeks after surgery it can be classified as early postoperative infection.
• Early postoperative infections are typically (but not only) caused exogenously by highly virulent microorganisms such as Staphylococcus aureus or gram-negative bacilli. Clinical signs of infection present early after implantation.
Step 2: Clinical symptoms and physical examination

- In early postoperative infections local signs of prosthetic joint infection may present several days or weeks after surgery (up to 4 weeks). Therefore daily targeted examination of the soft tissues at surgical site is important.
- Postoperative complications such as wound healing problems or haematoma must be actively ruled out. Patients need to be educated to report any aggravation immediately.
- If wound discharge continues beyond 5–7 days after surgery (risk for secondary infection from outside) or reappears within 4 weeks after surgery infection should be suspected. Imminent surgical revision with exchange of mobile parts is strongly considered.

Step 3: Imaging

- X-ray is used to rule out other possible reasons for problems with the prosthesis e.g. periprosthetic fractures or dislocations.
- In early postoperative infections due to the rapid progress of the infection there are often not yet signs for loosening.

Step 4: Laboratory Diagnostics

- CRP can be elevated because of wound healing after intervention or any infection including but not only surgical site infection (unspecific).
- Should CRP level do not steadily decrease after surgery infection must be suspected.
- A serial determination of CRP is needed to evaluate a possible postoperative infection.

Step 5: Preoperative microbiology and histopathology

- The number of leukocytes is always high after surgery. In early postoperative infection puncture of the joint is not a relevant diagnostic option.
- It is important to start the surgical treatment fast so the infection cannot spread to other joints, regions or organs.
- Remember to take at least blood cultures before starting the antibiotic therapy.
Step 6: Intraoperative microbiology and histopathology

- Intraoperative diagnostic methods (tissue biopsy of at least three specimen and sonication of the removed mobile parts of the prosthesis) should be used to verify the diagnosis and facilitate a targeted antibiotic therapy.
- Early postoperative PJI can become chronic if antibiotics are administered empirically.

Step 7: Treatment and postoperative follow-up

- In case of an early postoperative infection is suspected retention of the prosthesis is possible if surgery was less than 4 weeks ago. Then a surgical debridement and exchange of mobile parts of the prosthesis is performed.
- The goal for the diagnosis and treatment of early postoperative infections should be the retention of the prosthesis if possible. It is important to act fast.
- If one debridement is insufficient (approx. 20%) a second debridement is needed again accompanied by the change of all mobile parts. Successful management of infection needs a team. PJI always requires a combination of surgery and antibiotic therapy. Treatment must be adapted to the individual clinical situation.

LEARNING POINT

In case of early postoperative infections it is important to act fast as retention of the prosthesis is only possible within the first 4 weeks after surgery and to avoid the spread of the infection.

Checklist “Periprosthetic Joint Infection”

Diagnostics in PJI: How to do it right?

Biofilm

- Extend the culture time of any microbiological sample to 10–15 days due to reduced bacterial growth in the biofilm. Because of the sessile form bacteria often can’t be found in tissue samples or synovial fluid. Consider sonication of the explanted prosthesis in case of revision surgery to improve sensitivity of the culture of samples.
• Due to reduced bacterial growth implant loosening may be delayed and can be radiological visible only after three or more months.
• Only early biofilms are possible to eradicate with antibiotics, an infected implant with formed mature biofilm is not possible to retain.
• For cure of an implant-associated infection antimicrobial treatment needs to be active against biofilms.
• For the diagnosis of PJI teamwork between surgeon, microbiologist and infectiologist is crucial.

History

• Risk factors and the interval to primary surgery (or previous revision surgery) give first hints on the type of possible infection.
• If a prosthesis gets infected up to 4 weeks after surgery it can be classified as early postoperative infection. Early postoperative infections are typically (but not only) caused exogenously by highly virulent microorganisms such as Staphylococcus aureus or gram-negative bacilli.
• Main risk factor for haematogenaous infection of orthopedic prosthesis is bacteraemia (caused mostly by skin inflammation, lunge inflammation, urinary tract infection, intestinal infection or tooth infection). The risk of haematogenous infection exists throughout life and is cumulating over the years.
• The crucial time period for developing low-grade PJI typically lies between three months and three years after surgery.

Clinical diagnostics

• Consider any painful joint replacement to be infected until proven otherwise.
• If wound discharge continues beyond 5–7 days after surgery (risk for secondary infection from outside) or reappears within 4 weeks after surgery infection should be suspected. Therefore daily targeted examination of the soft tissues at surgical site is important. If infection is suspected it is important to act fast. Imminent surgical revision with exchange of mobile parts is strongly considered.
• Remember that a patient may have low-grade or chronic infection with no or only minor clinical signs of infection.
• Chronic PJI is almost never complicated by a sepsis syndrome. Therefore, you have sufficient time for a thorough diagnostic workup.
• Especially in low-grade or chronic PJI further measures are needed for diagnosis, in particular a synovial fluid leukocyte count and differential of the aspiration fluid.
Imaging

- Radiological signs of implant loosening cannot be detected until three or more months after infection.
- Remember that the absence of radiological signs does not exclude infection.
- Conventional radiographs are sufficient as first imaging procedure. In complex situations other imaging techniques should be discussed.
- A negative bone scintigraphy scan excludes infection with high probability due to its excellent sensitivity, but a positive result requires further testing.
- No imaging methods can differentiate between septic and aseptic cases.
- X-ray is used to rule out other possible reasons for problems with the prosthesis e.g. periprosthetic fractures or dislocations.
- In haematogenous PJI if a patient has more than one joint prosthesis it is important to check all of them accurately using scintigraphy, PET or joint aspiration.

Laboratory diagnostics

- Remember that no inflammatory marker test is sufficiently sensitive or specific enough to definitively diagnose or exclude PJI alone.
- A CRP value below the cut-off helps you to rule out infection in acute situations. Should CRP level do not steadily decrease after surgery infection must be suspected.
- In chronical infections values can be within the normal range.
- Reevaluate a patient within 3 months who is at lower probability for PJI and without planned reoperation but who has abnormal CRP levels.
- In any case you should prefer serial post-operative measurements over single determinations.
- A high CRP level (between 50 and 400 mg/l) is typical in case of haematogenous infection. Due to the bacteraemia not only CRP levels but all biomarker are elevated. Should CRP/biomarker levels do not steadily decrease after treatment other infectious foci should be excluded (septic thrombosis, endocarditis, other bone or joint infection, e.g. vertebral osteomyelitis).

Joint fluid aspiration

- Ensure cooperation with a microbiologist specialized in orthopaedic infections (orthopaedic microbiology service).
- Synovial fluid leukocyte count and differential are the most important preoperative diagnostic tests for chronic PJI.
- Remember that the cell count is not significant up to six weeks postoperative and for patients with rheumatic diseases or leukopenia.
• Allow antibiotic washout for at least 2 weeks before sampling.
• Aspirate at least 1–2 ml synovial fluid from each of 3 different regions.
• Perform the aspiration under strictly aseptic conditions to prevent contamination.
• Synovial fluid leukocyte count must be performed within 24 hours in a vial containing anticoagulants.
• In case of negative culture but high suspicion for infection, consider repeating aspiration.

Preoperative diagnostics

• No single test, but a combination of different diagnostic studies is usually required to diagnose PJI.
• Synovial fluid leukocyte count and differential are the crucial preoperative tests.
• In preoperative diagnostic many microorganisms often can’t be identified. But: Positive microbiology is not compulsory for diagnosing PJI.
• Stop antibiotics at least two weeks prior to aspiration (if not 20–30% false-negative results in culturing are to be expected)
• If clinical suspicion persists despite negative test results, surgery for tissue sampling, sonication of prosthesis and culture should be performed.
• Remember to take at least blood cultures before starting the antibiotic therapy.
• Intraoperative sampling
• Ensure cooperation with a microbiologist specialized in orthopaedic infections (orthopaedic microbiology service).
• Stop any antimicrobial therapy ≥ 2 weeks before intraoperative tissue sampling.
• Obtain ≥ 3 different tissue specimens for culture.
• Take additional ≥ 5 tissue samples for histopathological studies, polymorphonuclear cell count and consider intraoperative frozen section histology.
• The number of required samples is based on the class of infection. If low grade infection is suspected, five or more samples are needed
• Consider sonication of removed prostheses for improved diagnosis of biofilm infection.

Sonication

• Sonication of the implant and microbiological analysis of the sonication fluid is the easiest and most efficient method for intraoperative diagnosis of PJI and identification of the causative microorganism.
• The sensitivity is particularly improved in patients having previously received antibiotics, due to better survival of bacteria in biofilm.
• Place the implant compounds in sterile, solid and air-tide container and transport them immediately to the microbiological laboratory.

Intraoperative diagnostics

• Ensure cooperation with a microbiologist specialized in orthopaedic infections (orthopaedic microbiology service).
• Culture of tissue samples is the gold standard for intraoperative diagnostics.
• Consider sonication of the implant to improve sensitivity of the microbiological analysis.
• Request prolonged culture incubation of 7 to 14 days or special diagnostic methods like PCR or mass spectrometry to detect slow growing bacteria (e.g. Propionibacterium acnes).
• An increase of diagnostic validity is given by the combined interpretation of sonication findings and histopathological consensus-classification.

Treatment and postoperative follow-up

• In case acute PJI is suspected retention of the prosthesis is possible if surgery was less than 4 weeks ago or to onset of symptoms is less than three weeks ago. Then a surgical debridement and exchange of mobile parts of the prosthesis is performed.
• If one debridement is insufficient (approx. 20%) a second debridement is needed again accompanied by the change of all mobile parts.
• Successful management of infection needs a team. PJI always requires a combination of surgery and antibiotic therapy. Treatment must be adapted to the individual clinical situation.