Diagnosis of bone and joint infections

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Abstract

Bone and joint infections are common worldwide and cause considerable morbidity for the patient. Despite recent advances, they are difficult and expensive to treat. Regardless of the infection type (septic arthritis, osteomyelitis, fracture-related infections, or periprosthetic joint infection), patients may suffer from chronic ill health, multiple revision surgeries and prolonged hospital stay. An accurate diagnosis is the first step for successful treatment and infection control. However, due to the lack of a single test providing 100% accuracy, interdisciplinary teamwork is needed to diagnose bone and joint infections more precisely. Nevertheless, the diagnosis remains very challenging, especially in infections caused by low virulence organisms. This review will describe the diagnostic methods for septic arthritis, osteomyelitis, fracture-related infections and periprosthetic joint infections in current use in clinical practice.

Keywords diagnosis; fracture-related infections; histology; microbiology; osteomyelitis; periprosthetic joint infections; septic arthritis; tissue culture

Septic arthritis

Bacterial septic arthritis (infectious, pyogenic, suppurative, or purulent arthritis) in adults is an uncommon but serious emergency for physicians and surgeons dealing with musculoskeletal disorders. It affects 2–10/100,000/year of the normal population but is more frequent in hospital patients. Joint sepsis follows arthroscopic surgery in between 0.1 and 0.4% of cases. The most common portal of bacterial entry into the affected joint is via haematogenous spread. In patients with a bacteraemia, microorganisms can enter the joint due to a lack of protective basement membrane of the highly vascularized synovial lining. Rare causes can be direct local spread of a metaphyseal osteomyelitis into the joint or inoculation after trauma, surgery or intra-articular injections. The integrity of the joint capsule is destroyed and pathogens can penetrate the joint. An acute inflammatory reaction is induced and inflammatory cytokines and proteases lead to destruction of the joint. The degree of cartilage destruction is determined by the length of time between infection and treatment and by the nature of the infecting organisms.

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A delayed or inadequate diagnosis and treatment of a monoarticular septic arthritis can cause irreversible joint destruction, permanent loss of joint function, or even death. Therefore, an accurate and early diagnosis in combination with rapid and effective interventions are crucial for treatment success. However, a single test with a 100% accuracy does not exist for diagnosing septic arthritis. In 1976, Newman published a combination of criteria to define septic arthritis.[1] At least one of the four criteria has to be present to diagnose septic arthritis. However, the Newman criteria do not include the leukocyte count and differential, one of the most important diagnostic tests in the assessment of acute arthritis in the practice of the last decade. Therefore, modified Newman criteria (Table 1) involving the synovial fluid white blood cell count and percentage of polymorphonuclear neutrophils have been added in recent years.

Diagnostic methods

Medical history: a good survey of the medical history identifying risk factors can help to suggest a diagnosis of septic arthritis and the causative microorganism. Native joint infection is most common in neonates, the elderly, or in those with concomitant medical conditions. Risk factors include: pre-existing joint diseases such as rheumatoid arthritis, gout, pseudogout, osteoarthritis, lupus erythematosus, trauma and recent surgery. Among these, rheumatoid arthritis shows the highest risk for bacterial arthritis due to the combination of joint destruction, immunosuppressive medications, poor skin condition and intra-articular injections. In addition, patients with rheumatoid arthritis have a higher risk to develop an infection in more than one joint. The functional outcome is often worse, and mortality can be high. Septic arthritis can be misdiagnosed as a flare-up of inflammatory joint disease, so a careful approach to diagnosis is essential in these patients.

Other risk factors are the traditional risk factors for bacteraemia: immunosuppressed patients (systemic steroids and other immunosuppressive medications), patients admitted to hospital (especially those who have invasive surgeries), patients with urinary catheters or intravascular devices. In these cases, the focus of infection should be sought (e.g. by echocardiography for endocarditis). Diabetes mellitus, obesity, recent joint surgery, skin diseases (psoriasis, eczema, skin ulcers), end-stage renal disease, cirrhosis, intravenous drug abuse, previous intra-articular corticosteroid injections, and human or animal bites (often causing polymicrobial infections) are associated with a bacterial native joint infection.

The duration and nature of the clinical symptoms may also give an indication of the causative microorganism: patients infected by a typically virulent *Staphylococcus aureus* mostly report a prompt and acute onset of severe pain, swelling, erythema, and stiffness of the joint. This occurs alongside systemic upset, with pyrexia, tachycardia, sweating and rigors in about half of all patients. However, these symptoms can be absent, especially in elderly patients. Septic arthritis caused by low virulence organisms or mycobacteria commonly present without systemic upset and with more indolent mild symptoms in the joint, which develop over weeks or months.

Clinical examination: the diagnosis of septic arthritis is primarily clinical. The most common presentation is an acute onset

Modified Newman criteria for the diagnosis of septic arthritis

1. Isolation of a pathogenic organism from an affected joint
2. Isolation of a pathogenic organism from another source (eg, blood) in the context of a hot red joint suspicious of sepsis
3. Typical clinical features and turbid joint fluid in the presence of previous antibiotic treatment
4. Post-mortem or pathological features of septic arthritis
5. Elevated synovial fluid leukocyte count (>50,000 cells/μl) or polymorphonuclear neutrophils (>90%)

Table 1

(1–2-week-week history) of pain, joint swelling, effusion, increased joint temperature (in comparison to the contralateral site), erythema and limited range of motion of the affected joint. Due to the soft tissue coverage, swelling and joint effusion may not be identifiable at the hip or shoulder, which sometimes makes diagnosis difficult.

Typically, one of the large joints of the lower leg are affected. The most common site of septic arthritis is the knee followed by hip, shoulder, wrist and ankle. Generally, septic arthritis is monoarticular. However, in about one-fifth of cases, more than one joint can be affected, especially in patients with multiple co-morbidities, rheumatoid arthritis, extended bacteraemia and sepsis.

Serum analysis: in patients with systemic signs of inflammation (e.g. fever, rigors), blood should be taken for microbiological culture before antibiotics are given. In a septic patient, this may be the only opportunity to culture organisms off antibiotic therapy.

Systemic inflammatory markers, such as serum white blood cell counts, C-reactive protein or erythrocyte sedimentation rate, are neither sensitive nor specific in the diagnosis of septic arthritis. They cannot distinguish a bacterial joint infection from other forms of acute arthritis or other sources of infection.

Imaging: ultrasound scanning is valuable in confirming the presence of a joint effusion and synovial inflammation, particularly in the hip and shoulder. It also facilitates aspiration of joint fluid and synovial biopsy.

Radiographs, MRI, CT and scintigraphy cannot distinguish between septic and other forms of acute arthritis. However, they can help to evaluate the extent of inflammation and joint destruction.

Radiographs may show joint space widening, periarticular fat pad displacement, or erosive changes. Generally, MRI is the method of choice. The involvement of the surrounding soft tissues can be precisely evaluated. The coexistence of osteomyelitis in adjacent bone, abscesses and the tracking of purulent fluid into surrounding soft tissues can be assessed. This may help the surgeon to guide and plan treatment (Figure 1).

Microbiological culture: the presence of microbial growth in the synovial fluid is the gold standard diagnostic test for septic arthritis. Also, the choice of antimicrobial agent is based on the microbiological result and antibiogram.

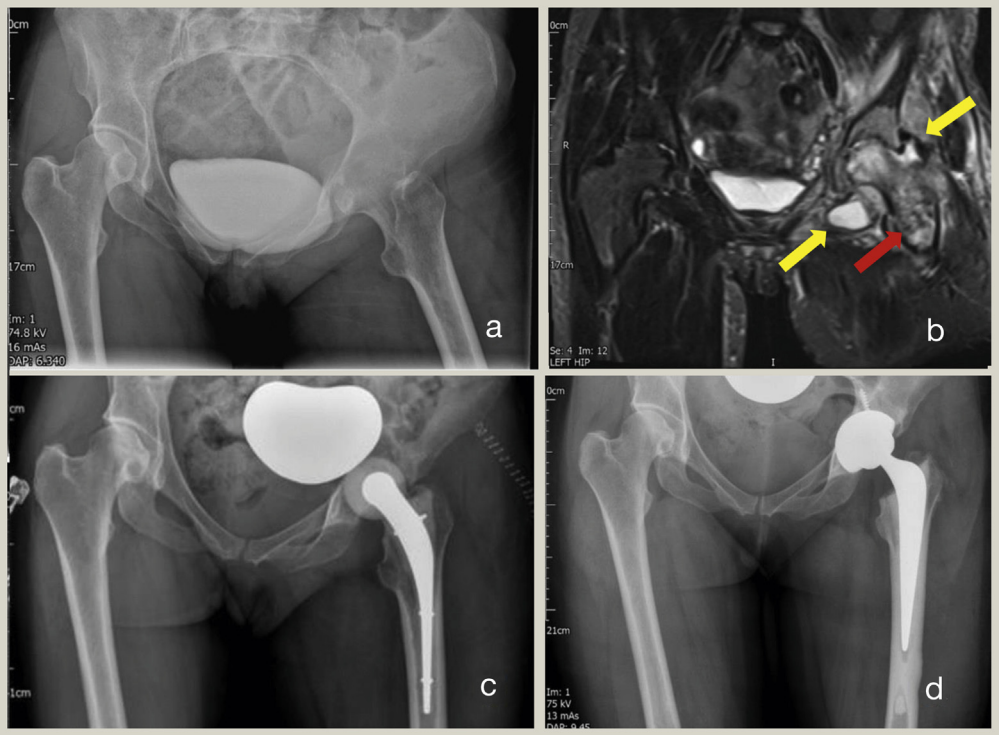

Figure 1 (**a**) X-rays of a 33-year-old female patient with septic arthritis of the left hip due to intravenous drug abuse. None of the six samples sent for microbiological analysis showed growth after 10 days. (**b**) The T2-sequences of the MRI shows effusion (yellow arrows) of the left hip joint and oedema (red arrow) of the femoral head and neck. A two-stage procedure for a primary total hip arthroplasty was performed. (**c**) An X-ray after the first stage (a polymethyl methacrylate (PMMA)– cement spacer was implanted) and (**d**) shows an X-ray of the pelvis after the second stage and reconstruction of the hip with a total hip prosthesis (the cup was fixed with a screw).

Synovial fluid aspiration of the affected joint should be performed under sterile conditions. Prior to needle insertion a small skin incision should be made, to avoid the inoculation with skin flora. Ideally, the joint should be punctured before initiating antimicrobial treatment to increase the identification rate of the causing microorganism. However, in cases with severe sepsis, antimicrobials should not be delayed prior to joint puncture.

The collected synovial fluid samples should be cultured for at least 10 days. Virulent pathogens (such as *S. aureus*) may be cultured within 1 day, but low-virulence organisms (e.g. *Cutibacteria* spp.) may require up to 14 days. *Mycobacteria* may take even longer. If the suspicion of an unusual organism exists (due to clinical features), the laboratory needs to be informed, as specific culture techniques are needed. For some *Mycobacteria* low-temperature cultures are necessary. In immune-compromised patients, or in those with extensive recent antimicrobial therapy, the samples should be investigated for fungi or other unusual organisms.

For the most common infecting microorganisms (Table 2), synovial fluid culture alone, has a reasonable accuracy. Inoculation of synovial fluid into blood culture bottles gives a higher sensitivity compared to traditional agar plate cultures. Accuracy can be improved by culture of synovial tissue, especially when there is infection with low virulence pathogens and the microorganism load may be small. Hence, if an operation is performed, at least five tissue samples should be sent for microbiological analysis. In recent decades, the identification of bacterial DNA and RNA is advocated and has shown promising results in the literature. It is not yet universally established, but it may well be the diagnostic method in the future.

Synovial fluid analyses: the collected synovial fluid should also be analysed for white blood cell count including the percentage of polymorphonuclear neutrophils. For the evaluation of the white blood cell count, the collected synovial fluid should be inoculated into ethylenediaminetetraacetic acid (EDTA) tubes. The tube should be gently agitated manually to avoid clotting of the samples. While the evaluation of white blood cell count has become obligatory in the diagnosis of septic arthritis, the cut-off value remains controversial. However, many studies recommend a cut-off of >50,000 cells/μl. Below this level, the infection rate is markedly reduced. However, in some cases, especially low-grade infections, septic arthritis can be present without an elevated white blood cell count. On the other hand, gout and pseudogout can also cause elevated white blood cell counts of this magnitude.

The percentage of polymorphonuclear neutrophils (granulocytes) in synovial fluid can also provide useful information. A cut-off of >90% is sensitive for the presence of infection. Cut-offs for the white blood cell count and the percentage of polymorphonuclear neutrophils are unreliable in immune-compromised patients or patients with leukopenia or neutropenia.

The synovial fluid samples should also be examined for crystals. Crystal arthritis can mimic the symptoms of septic arthritis. For crystal analysis, the samples should be processed immediately or stored at room temperature to avoid artificial crystal formation in the fridge. Laboratories with adequate quality control and standardization are important.

The assessment of Gram stains of synovial fluid can be helpful when positive. It may provide a rapid indication of the type of the infecting organism. However, the sensitivity has been shown to be poor, at around 50%. Hence, this diagnostic method can not be recommended for evaluation of septic arthritis alone.

Histopathology: histopathological analysis of synovial tissue samples completes the diagnosis of septic arthritis. In culture-negative cases, histology can confirm a bacterial infection of the native joint by the presentation of acute or chronic inflammatory cells. Caseating granulomas may confirm tuberculous infection and fungal hyphae or filamentous bacteria may be seen directly on histology. In general, at least two tissue samples from suspicious areas of infection should be collected during the operation. If an operation cannot be performed (due to significant co-morbidities) and synovial fluid cultures are negative, an ultrasound-guided biopsy of the synovia can be done. The samples should be sent for microbiological and histological analysis. The results can help the infectious disease specialist to guide the antimicrobial treatment for suppression.

Most common microorganisms in septic arthritis

- ***Staphylococcus aureus***
- **Streptococci** (especially Group B, *Strep. pneumoniae*)
- Coagulase-negative staphylococci (*Staphylococcus epidermidis*)
- Gram-negative bacilli (*Escherichia coli*, Enterobacteriaceae, *Haemophilus influenzae*)
- Anaerobes (*Cutibacterium* spp., *Bacteroides*, *Actinomyces*)
- *Neisseria* (*N. gonorrhoeae*, *N. meningitidis*)
- *Mycobacteria* (*M. tuberculosis*)
- Fungi

Table 2

Osteomyelitis and fracture-related infections

Osteomyelitis is an inflammatory condition involving the cortex and the medulla of bone. There are two mechanisms which can cause osteomyelitis: The infecting pathogen can be blood-borne (**haematogenous osteomyelitis**) or it enters the bone through an open fracture, a skin lesion, or a bone operation (**contiguous focus osteomyelitis**). Both aetiologies can lead to a **chronic osteomyelitis** which can produce ongoing pain, a persistent fistula with drainage and chronic ill health. This can be associated with recurrent need for medical treatment. Patients with chronic osteomyelitis can suffer from social isolation, unemployment, and depression. Therefore, an accurate diagnosis and treatment is essential.

However, the diagnosis can be difficult due to a lack of a single accurate test. There are no agreed standardized diagnostic criteria for haematogenous osteomyelitis. The European Bone and Joint Infection Society (EBJIS) and the AO Foundation (Association for the Study of of Internal Fixation) defined criteria for fracture-related infections (FRI),[1] which can also be used for osteomyelitis. They defined four confirmatory criteria and at least one criterion has to be fulfilled to diagnose an FRI (Table 3). In addition, a list of suggestive criteria was also defined, which

European Bone and Joint Infection Society (EBJIS) criteria for fracture-related infections

Confirmatory criteria

1. A sinus tract communicating with the bone or the implant
2. Purulent drainage from the sinus or pus during surgery
3. Phenotypically indistinguishable pathogens identified by culture from at least two separate deep tissue/implant specimens
4. A positive histopathological analysis

Suggestive criteria

a. Clinical signs (pain, local redness, swelling, increase local temperature, fever)
b. Radiological signs (bone lysis, implant loosening, sequestration, no progression of bone healing, periosteal bine formation)
c. A single positive microbiological results
d. Elevated serum inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, white blood cells)
e. Persistent, increasing or new-onset wound drainage, beyond the first days postoperatively, without solid alternative explanation
f. New-onset of joint effusion which can be an adjacent septic arthritis

Table 3

require further investigations in order to look for confirmatory criteria (Table 3).

In 1983, Cierny and Mader designed a classification for chronic osteomyelitis which still remains the most widely used classification. It is based on four anatomical types (I: medullary osteomyelitis; II: superficial osteomyelitis of the outer part of the bone cortex; III: medullary bone and cortex limited to the circumference of the bone; IV: diffuse osteomyelitis plus skeletal instability) of osteomyelitis and three physiological groups of patients (A: healthy patients, B: patients with impairments affecting the ability to heal [B_l: local impairments; B_S: systemic comorbidities; B_{LS}: local and systemic impairments], C: patients in which operation is contraindicated).[2]

Diagnostic methods

Medical history: the medical history is essential in the diagnosis of osteomyelitis and FRI. A survey of the chronological sequence and progress of the symptoms should be made. Infection begins acutely and will progress to chronicity with dead bone and a recurrent and relapsing course. In some patients, haematogenous osteomyelitis arises in childhood and may persist for decades. During their life, they experience many flare-ups with breakdowns of the skin and discharge of pus (sinus tract). Under antimicrobial suppression the wound and the fistula can heal. Stopping antimicrobials can provoke a further infection flare-up. However, chronic osteomyelitis can also be quiescent for many years.

Further relevant aspects are previous conservative and surgical treatments, courses of antimicrobial treatment, flare-ups, and risk factors. Local risk factors in the limb are previous fractures, especially open fractures, previous operations and retained foreign material/implants. Systemic risk factors are intravenous drug abuse, immune-suppression, malignancy, and sickle-cell disease.

The examiner should also ask about recent infections (e.g. common cold, bronchitis, or pneumonia), fever or rigor to discover a bacteraemia and systemic involvement. These are common in acute osteomyelitis but often absent with chronicity.

Clinical examination: a sinus tract communicating with the bone or metalwork and persistent discharge of the wound represent definitive criteria of infection. In some cases, the soft tissue defect can be so large that the bone or metal work ('mirror sign') is visible. Other local features of an osteomyelitis or FRI are localized pain, unilateral swelling, erythema, increased limb temperature and reduced range of movement. However, in chronic infections symptoms may be subtle or can be absent completely. Most common signs in these patients are diffuse or non-specific pain, minimal swelling, local tenderness or a small patch of increased temperature. However, the examiner should investigate the skin and soft tissues for old healed sinuses, scars from previous operations, soft tissue abscesses, or active discharging sinuses.

The adjacent joints should also be examined to exclude an adjacent septic arthritis. In rare cases, the osteomyelitis may spread into a joint, especially in pre-pubertal patients with acute haematogenous osteomyelitis. In patients with intraarticular fractures or after minimal-invasive surgeries (e.g. internal fixation for distal femoral fractures or ankle fractures), screws or plates can perforate into the joint and hence destroy the integrity of the joint capsule, allowing ingress of bacteria.

Systemic symptoms of acute infections are fever, sweats, rigor, anorexia and/or malaise. In chronic infections, the patients may suffer from long-term ill health, fatigue, weight loss, malaise, and/or depressed mood.

Serum analysis: in general, serum is analysed for inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate or white blood cell count. However, they are non-specific to confirm the diagnosis of osteomyelitis or fracture-related infections. While these parameters may be elevated in acute infections, they are often normal in chronic infections. They can be used as suggestive signs in the diagnosis of osteomyelitis and FRI, prompting further investigation.

If patients show systemic signs of inflammation (fever), blood cultures should be taken. Blood serology can also diagnose atypical infections with *Brucella*, *Bartonella* or *Spirochaetes*.

Imaging: imaging may suggest but cannot confirm or exclude an osteomyelitis or FRI. It should be used prior to surgery to help planning the surgical approach and reducing the extent of the procedure.

Plain X-rays, generally taken in two views (AP and lateral), remain the initial imaging of choice. In the early phase of acute infection, X-rays are normal and show no overt changes. However, suggestive signs of infection such as bone sequestrum (devascularized/sclerotic fragments), progressive bone loss, cloaca, infection callus (involucrum), a broadened fracture gap, bone lysis, and loosening around the fracture fixation devices may appear, especially in chronic infections. Due to disuse, general osteopenia may be present over several weeks. In these osteopenic cases, cortical

bone which remains without osteopenia is likely to be avascular and dead. If available, a comparison with previous films is important to evaluate the extent of progression.

If no metal implant is present, magnetic resonance imaging (MRI) is the modality of choice. It provides detailed information about the extent of bone and soft tissue infection: inflammatory intramedullary changes, medullary abscesses, periosteal involucrum, sequestra (although not as well as CT), cloacae in the cortex, subperiosteal collections, the presence of abscesses and fluid collections in the soft tissues surrounding the affected bone, as well as the expansion and location of sinus tracts. However, limitations are the over-estimation of the margins of intramedullary infection due to bone oedema obscuring the extent of active infection and the fact that the presence of metal implants leads to complex artefacts. In patients with implants, MRI with metal artefact reduction software (MARS) is preferred.

Computed tomography gives excellent demonstration of the extent of bone necrosis, sequestra (especially visualization of small sequestra), bone lysis, and loosening of the implant. It may help in decision-making to define the extent of necessary excision. However, it lacks accurate visualization of soft tissues and sinus tracts. The combination of a CT with a nuclear scan (single-photon emission computed tomography with CT (SPECT-CT) or ^{18}FDG-positron emission tomography with CT (^{18}FDG-PET-CT)) improves the assessment of the extent and may allow better anatomical definition of infection. However, in the early period after surgery or injury (<six weeks), the scans are difficult to interpret.

Ultrasound scanning allows visualization of soft tissue abscesses and joint effusion. It is also used for biopsies. However, biopsies in chronic osteomyelitis can be false-negative due to sparse distribution of the microorganisms throughout the area of abnormal tissue (Figures 2 and 3).

Microbiological culture: when abscesses or fluid collections in the soft tissue are present, aspiration can be performed either ultrasound-guided or without additional imaging. Occasionally, CT-guided biopsy may be needed for inaccessible regions. The preoperative microbiological analysis may help to guide antimicrobial treatment during and after surgery.

However, the gold standard diagnostic test in osteomyelitis or fracture-related infections is culture from deep tissue samples collected during an open surgical procedure. At least 5 tissue specimens should be taken at the beginning of the operation before extensive debridement and before the use of suction and

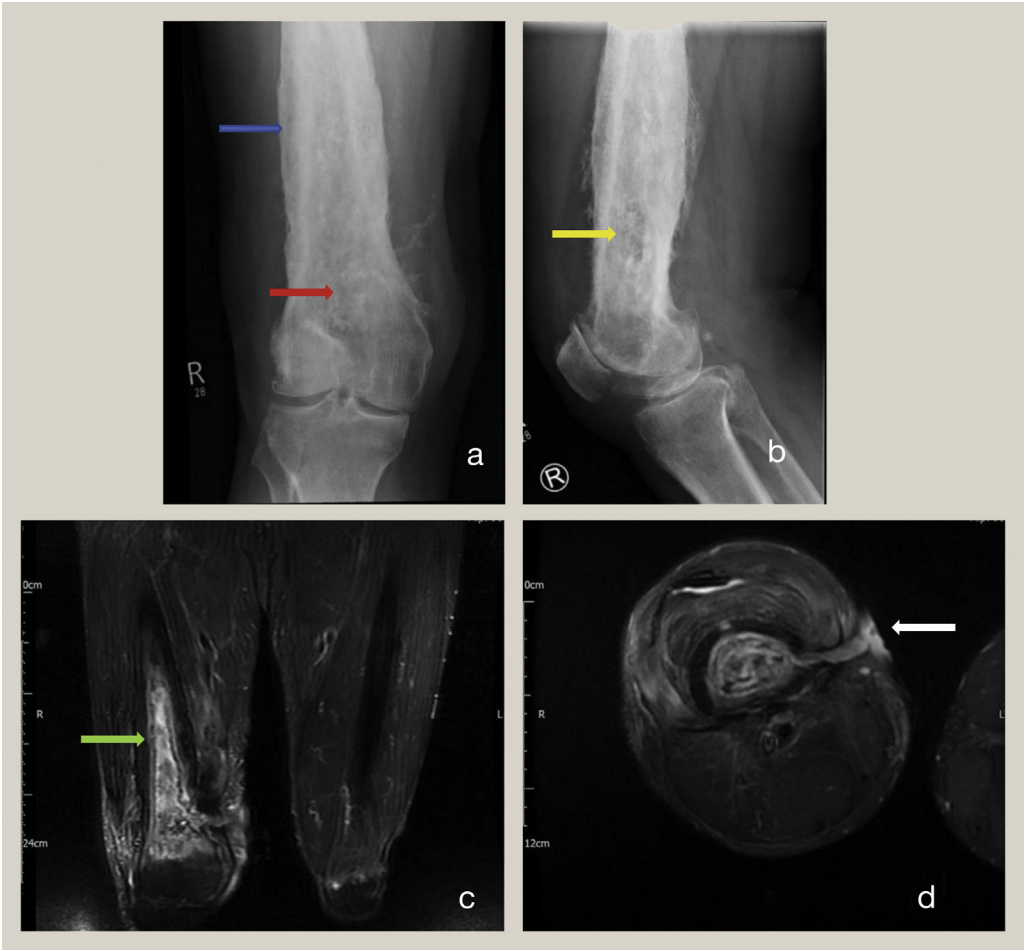

Figure 2 Imaging of a 62-year (C-reactive pro-old male patient with a chronic osteomyelitis of the distal femur caused by *Staphylococcus aureus*. He had a 15-year history of ongoing discharging sinus tract in the medial aspect of his distal thigh. He had two previous excisions of infected bone, the first at the age of 13. **(a, b)** Anteroposterior and lateral views of the distal femur. A mature cortical thickening, combined with a new periosteal reaction (involucrum, blue arrow), central bone lysis (red arrow) and multiple small sequestra (yellow arrow) can be seen. The MRI (STIR sequence) shows in the coronal **(c)** and axial **(d)** views the corona sign (granulation tissue – fluid layer – endosteum; green arrow) and the medial sinus tract (white arrow).

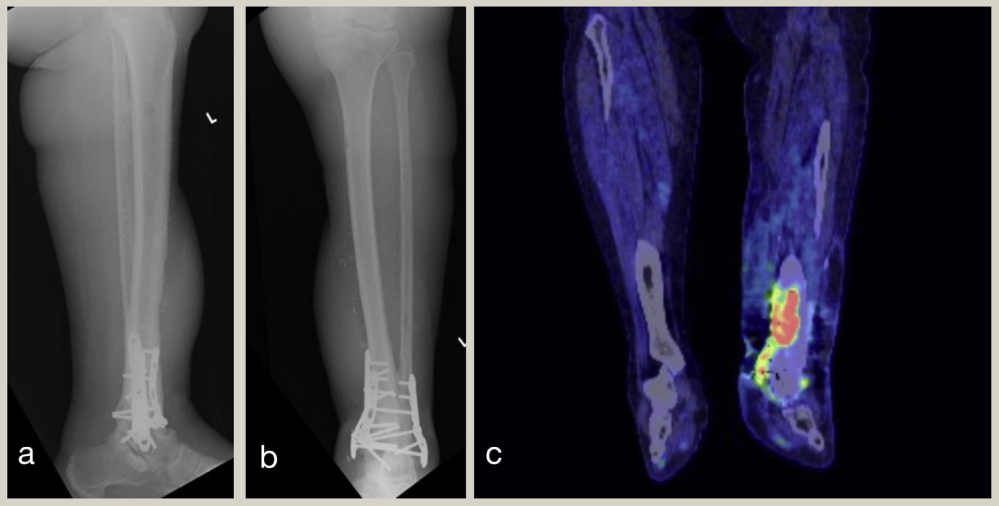

Figure 3 Imaging of a 56-year-old female patient with a previous leiomyosarcoma excision. After 5 years, she had a pathological fracture following radiotherapy which was fixed internally. Four years later she presented with a continuing sinus tract at her medial distal lower leg. In the anteroposterior **(a)** and lateral **(b)** X-rays some lysis was found around the front of the distal tibia and the superior surface of the talus adjacent to one of the plates which presents bone loss from infection. It is impossible to define the extent of the infection on these images. ^{18}F-Fluorodeoxyglucose (FDG)-positron emission tomography-CT **(c)** showed a markedly FDG-avid sinus tract extending from the anterior surface of the left lower leg and around distal tibial screws involving the anteromedial tibia at the same level with increased FDG uptake extending up the medullary cavity for 9 cm.

diathermy to minimize the risk of contamination. The sampling should be done with strict aseptic precautions. It is advisable to use new sterile instruments for each tissue specimen to avoid cross-contamination. The samples should be taken from the site of possible infection (necrotic tissue, sequestrum (necrotic bone fragment), tissue from the interface between bone and metalwork, samples from the fracture site or non-union, deep tissue samples from the adjacent soft tissue). The specimens should be cultured for aerobic and anaerobic microorganisms for at least 14 days. While highly virulent microorganisms (*S. aureus, Escherichia coli*) show growth after a short period of time (1–2 days), the duration can be prolonged in low virulence organisms (*Cutibacterium* spp.). If an atypical organism is suspected by the clinical or radiological features, the laboratory should be warned to specify culture techniques.

The identification of a microorganism is hampered by the bacterial production of biofilm on non-living surfaces such as implants or devitalized bone fragments. The bacteria in these localized communities are in a stationary phase (persister cells) and metabolically quiescent. Therefore, these bacteria are sheltered from antimicrobial treatment, and the host immune system. In the last decade, sonication was introduced to disrupt biofilm and liberate the microorganisms by means of ultrasound.[3] Thereby, the detection rate and the harvest of organisms are enhanced. The combined evaluation of tissue cultures and sonication showed an even higher yield than one method alone.[4]

In recent years, attention has also been paid to genotypical analysis (DNA, RNA) of the tissues in the diagnosis of osteomyelitis and fracture-related infections. The results of whole genome sequencing of bacterial DNA and multiplex PCR are promising.[5,6] In the future, this bacterial detection method may be part of the diagnostic algorithm.

Best results for microbiological analysis will be obtained if the patients have not received any antibiotics for at least 14 days. Superficial swabs from sinuses or wounds show high contamination rates and are not recommended.

Table 4 shows the most common causing microorganisms of osteomyelitis and FRI.

Histopathological analysis: histopathological analysis supports the microbiological diagnosis. During surgery, at least two clean deep tissue samples should be collected for histopathological analysis. The samples should be taken from areas with high suspicion of infection. The samples should be interpreted by a pathologist experienced in musculoskeletal infections. In general, at least ten x400 magnification high-powered fields (HPFs) should be evaluated. The presence of more than five neutrophils per high power field represent a definitive infection, while the complete absence of neutrophils is almost always aseptic.[7] In addition, dead bone, active bone resorption and remodelling and the presence of small sequestra can be seen by the pathologist, especially in chronic osteomyelitis.

Some infections (for example tuberculosis or actinomycosis) can be directly diagnosed by histological assessment alone.

Periprosthetic joint infection

Periprosthetic joint infections (PJI) are the most feared complications after total joint replacements among orthopaedic

Most common microorganisms in osteomyelitis and fracture-related infections

- ***Staphylococcus aureus***
- **Coagulase-negative staphylococci** (*Staph. epidermidis, Staph. capitis*)
- Gram-negative bacilli (*Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae*)
- *Enterococcus* spp. (*E. faecalis, E. faecium*)
- Anaerobes (*Cutibacterium* spp.)
- Streptococci (*Strep. pyogenes, Strep. agalactiae*)
- Fungi (*Candida* spp.)

Table 4

surgeons. The incidence is likely to increase in the future due to a rising number of implants and increasing life expectancy. An increase in revision burden has to be anticipated.

About two-thirds of PJIs are due to the inoculation of micro-organisms during the primary implantation of the prosthesis. Other **contiguous** pathways are direct local spreading through an open fracture, a skin lesion, and direct contact with adjacent infections (septic arthritis, osteomyelitis, infected soft tissue). Some late infections are due to pathogens colonizing implants through **haematogenous** spread as mentioned before (septic arthritis section).

Diagnosis of PJI is very challenging, especially low-grade infections caused by low virulence organisms (*Staph. epidermidis, Cutibacterium acnes*) living in highly organized biofilms. Unfortunately, no single diagnostic test can deliver high sensitivities and specificities. Therefore, the Musculoskeletal Infection Society, the Infectious Diseases Society of America, and the European Bone and Joint Infection Society introduced different criteria for a better diagnosis of periprosthetic joint infections. The European Bone and Joint Infection Society (EBJIS) criteria showed a higher detection rate and better identification of low virulence organisms compared to the other two criteria.

According to the EBJIS criteria (Table 5) a periprosthetic joint infection is present, when at least one of the criteria applied.[8]

Diagnostic methods

Medical history: the exact onset of symptoms is immensely important for surgical decision-making (prosthesis retention (except exchange of mobile parts) vs total exchange of the prosthesis). Infection can present early (0–3 months), delayed (3–24 months) or late (>24 months) after implantation of the prosthesis. In general, early infections arise due to inoculation of bacteria at the time of primary surgery and are caused by highly virulent organisms (*Staph. aureus or E. coli*). They present acutely, with a short duration of symptoms, often with systemic upset. Occasionally, early infections are due to haematogenous spread from other infective foci (endocarditis, respiratory or urinary tract infection, dentition, intravascular devices (pacemaker, central line, IV cannulae), abdominal abscess, spondylodiscitis, etc.).

Infection can also present in a more indolent fashion, usually after 3 months from surgery. These delayed infections are usually caused by low virulence organisms (*C. acnes* and coagulase-negative staphylococci (e.g. *Staph. epidermidis*), inoculated at the time of primary surgery. Symptoms develop slowly, usually over more than 4 weeks.

Late infections are almost always haematogenous in origin and can be due to a wide range of organisms. They can present acutely, or insidiously over many months.

Clinical examination: patients with an early or haematogenous PJI typically suffer from acute joint pain, erythema, effusion, swelling, high local temperature and reduced range of motion of the affected joint. If there is a prolonged discharge (more than 7 days) immediately after implantation an ongoing infection is most likely.

In haematogenous infections the patients can also suffer from systemic bacteraemia symptoms such as fever, sweats, rigor, anorexia and/or malaise.

In delayed PJI, the onset of symptoms is insidious and progresses slowly. Symptoms can be very non-specific making the diagnosis difficult. Local signs can be vague pain, minimal effusion, local tenderness, and small patch of increased temperature. On the other hand, a discharging sinus tract communicating with the prosthesis can be seen in some cases. All agree that the development of a fistula is a clinical feature which is a definitive criterion of infection.

Systemic symptoms of chronic PJI are long-term ill health, fatigue, weight loss, malaise, and depressed mood.

For planning the revision surgery, the surgeon should also investigate the surrounding soft tissue and skin for scars from previous operations, soft tissue abscesses, and fluid collections.

Serum analysis: the value of serum parameters in the diagnosis of periprosthetic joint infections is limited. They are non-specific: if serum white blood cell count, C-reactive protein, erythrocyte sedation rate are elevated, PJI can be present but also other types of infections can cause the increase in these parameters. C-reactive protein is also non-sensitive, especially in PJI caused by low virulence organisms. In over 30% of low-grade infections, this protein is not elevated at all. Therefore, these parameters cannot be recommended as screening tests for PJI.

Some authors advocate the evaluation of serum D-dimer. One study showed promising results, but it is not universally accepted at present and further studies are needed.

Imaging: imaging is not included in any published criteria because of the inability to distinguish between septic and aseptic loosening. Nevertheless, it is essential for surgical planning. Plain X-rays may show loosening around the prothesis (Figure 3b), osteolysis, heterotopic ossification, and/or joint effusion. Ultrasonography will allow visualization of peri-articular collections and abscesses, together with joint aspiration. CT can provide a better evaluation of the extent of the osteolysis and bone loss. Patients with non-ferrimagnetic implants can also

European Bone and Joint Infection Society (EBJIS) criteria for periprosthetic joint infection

1. Macroscopic purulence around the prosthesis
2. Presence of sinus tract communicating with the joint
3. Abnormal synovial fluid leukocyte count and differential (>2000 leukocytes/μl or >70% granulocytes)
4. Significant growth of a microorganism from
   a. Synovial fluid
   b. Periprosthetic tissue
      ≥ 1 positive specimen in high-virulence organisms
      ≥ 2 positive specimens in low-virulence organisms
   c. Sonication culture of retrieved prosthesis components
      > 50 CFU/ml sonication fluid grew
5. Positive histopathology (defined as a mean of ≥23 granulocytes per 10 high-power fields, corresponding to type 2 or type 3 periprosthetic membrane)

CFU, colony-forming units.

Table 5

have MRI to evaluate the involvement of surrounding soft tissue (if necessary). However, MRI and CT have the disadvantage of producing artefacts in patients with implanted prostheses. Hence, they often provide less additional information.

There is no role for nuclear imaging in the early phase after implantation of a prosthesis. Simple isotope scanning (^{99m}Tc-labelled scintigraphy) is unhelpful, as accumulation of the tracer will be seen around a normal prosthesis for 1–2 years after primary surgery. After a few weeks, labelled white-cell scans may be able to diagnose infections, but the literature is controversial.

The combination of nuclear imaging with a localizing scan has been shown to be both sensitive and specific for diagnosis of PJI more than 4 weeks after implantation. SPECT-CT and ^{18}FDG-PET-CT have been investigated with good results. PET-CT has the advantage of shorter scanning times and better resolution but cannot distinguish tumour from infection.

Synovial fluid analyses: preoperatively, the evaluation of white blood cell count and the percentage of polymorphonuclear neutrophils in the synovial fluid is the most accurate method to diagnose PJI. The diagnostic levels of white cell count and percentage polymorphs are controversial but a concentration of >2000 white blood cells/μl and a percentage of >70% polymorphonuclear neutrophils confirms the presence of an infection, with a high degree of sensitivity. The synovial fluid is inoculated in EDTA tubes to avoid clotting of the specimen. In cases with high viscosity fluids, hyaluronidase can be added. In the early postoperative period (6 weeks), periprosthetic fracture, dislocation, crystal arthropathy and rheumatoid arthritis, may cause the leukocyte count to be falsely high.

Leukocyte esterase colorimetric test strips show good accuracy but are not as good as the direct evaluation of leukocyte count. In addition, this test method cannot be applied in specimens contaminated with blood (up to 30%) due to false elevation of the enzyme.

Microbiological culture: culture is the gold standard diagnostic method to identify the causative pathogen. If possible, any antimicrobial treatment should be stopped prior to specimen collection to improve the identification rate of microorganisms. Superficial swabs should not be used to avoid false detection rates. Table 6 illustrates the most common pathogens causing periprosthetic joint infection.

Preoperatively, synovial fluid samples should be microbiologically analysed to help decision-making before surgery. The aspiration should always be performed under sterile conditions. Ideally, an incision of the skin is done before inserting the needle to avoid inoculation of skin flora pathogens. The samples should be cultured for at least 14 days to increase the detection rate of low virulence microorganisms. Best results were found when synovial fluid samples were introduced in blood culture bottles. However, in up to 30% the culture can be negative although an infection is present.

Tissue cultures have a higher accuracy compared to synovial fluid cultures. At the beginning of the surgery (before extensive debridement and contamination of the surgical field), at least five samples should be collected from areas of possible infection (interface between bone and prosthesis, granulation tissue, synovia, necrotic bone, etc) under sterile conditions. New instruments (forceps, scalpel) for each sample are recommended to avoid cross-contamination. The specimens should be sent for microbiological and histopathological analysis.

Metal, ceramic or polyethylene implants can be sent separately for sonication. Care should be taken during their removal to prevent contamination by contact with the skin. Sonication fluid cultures showed a very high accuracy in diagnosing PJI and is less influenced by previous antimicrobial therapy.[9–11] By using ultrasound, pathogens are liberated from the biofilm in the sonication fluid, which then is used for further microbiological analysis. Sonication has been shown to have an increased detection rate of low virulence microorganisms. Inoculation of sonication fluid in blood culture bottles showed an even higher identification rate and also a reduced culture time, especially in low grade infections.

Histopathological analysis: tissue samples collected during revision surgery from areas with suspicion of infection should always be sent for histopathological analysis due to its very high accuracy. It is important to work together with a pathologist specialized in musculoskeletal infections who has experience in diagnosing PJI. Generally, samples are classified according to the Krenn and Morawietz classification.[12] In this classification four types of periprosthetic membranes are differentiated: (1) particle type (wear induced), (2) infectious type, (3) combined, and (4) indifferent type. Neutrophil count is assessed in 10 selected high power fields (x400) and infection is confirmed when a total of >23 neutrophils are seen. Due to the introduction of the CD 15 score a distinction between high virulence and low virulence pathogens can be made. While histopathological analysis has very high sensitivities and specificities the causative microorganism cannot be identified.

Another limitation is prolonged duration until results are available (1–4 days). When a PJI cannot be confirmed or excluded preoperatively, the surgeon relies on intraoperative tests such as frozen section for decision making (aseptic or septic revision surgery). In the hands of an experienced pathologist, frozen section showed an almost perfect concordance with permanent section. However, in many institutions frozen section is not available (Figure 4).

New diagnostic methods: in recent decades, synovial fluid alpha Defensin has been investigated intensively as a diagnostic marker for PJI. Controversial results are reported in the literature. The presence of alpha Defensin in the synovial fluid can be

Most common microorganisms in periprosthetic joint infection

- Coagulase-negative staphylococci *(Staph. epidermidis)*
- ***Staphylococcus aureus***
- Gram-negative bacilli (*Escherichia coli*)
- *Streptococcus* spp. (*Strep. pneumoniae*)
- *Enterococcus* spp.
- Anaerobes (*Cutibacterium* spp.)
- Fungi (*Candida* spp.)

Table 6

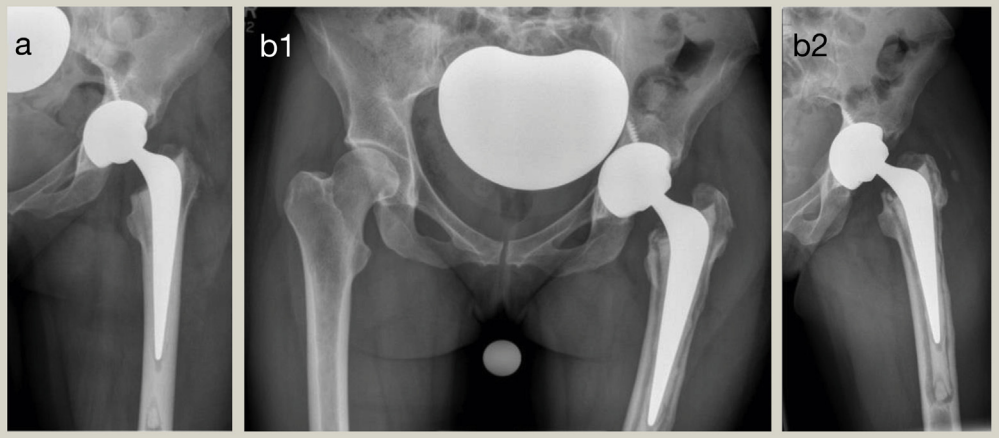

Figure 4 X-rays of the patient in Figure 1 with (a) her left total hip arthroplasty. No signs of loosening are visible. Two years later the patient had a relapse of intravenous drug abuse and presented with severe pain, elevated serum C-reactive protein (241.3 mg/litre), and positive synovial fluid culture (*Streptococcus agalactiae*). The X-rays after 2 years (b1+2) showed extensive loosening around the femoral stem and bone cement and early loosening at the lateral and proximal aspect of the acetabulum. This is an acute haematogenous infection.

measured by using an ELISA test or qualitatively by using a lateral flow test (which is quick − 10 minutes, and easy to use). Both tests showed similar results at trial with no statistically significant difference. The α-defensin tests are highly specific, but sensitivities low.[8,13] Hence, they can be used as confirmatory tests rather than screening tests.

PCR techniques for genotypical identification of pathogens (RNA, DNA) show promising results in the diagnosis of periprosthetic joint infections, especially low virulent microorganisms can be detected more precisely.[14,15] In addition, the identification rate in patients under antimicrobial treatment is higher compared to conventional culture. Nevertheless, these techniques are not universally accepted, although they may complement our diagnostic pathway in the future. ◆

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